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Editorial

Quote - - - Unquote

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The literature has grown so large of late that some of the time-honored practices in science are being modified. Perhaps we should take note of such modifications and consider whether they are or are not desirable.

When a scientific article was written in the past, it was customary to review all of the literature related to the subject and either refute or agree with what had been written, advancing, if possible, from that point. This practice has the merit of promoting the mosaic growth of a subject as an organic whole and of emphasizing the importance of every scientific worker regardless of his eminence or "genius." Today, the usual scientific article will quote only what the author happens to consider relevant or, perhaps, advantageous.

Let us for a moment consider the motivation for quotations. When a man becomes editor of a journal, the number of his articles quoted immediately trebles. The reason for this cannot be attributed entirely to the increased merit and interest of his work. Also, some authors think that omitting reference to certain papers is the best way to avoid polemics, however necessary such controversy may be in science. They are often too lazy or too busy to read all of the literature, especially the foreign literature, and may not know of the existence of certain papers. Some quotations, moreover, especially of prior similar efforts, may detract from the impression of originality which the author would like to give. Sometimes an author dislikes someone in his field personally, and so does not wish to "glorify" him in a paper. In addition, editors frequently exert pressure on authors to cut down the number of quotations, however relevant.

Now, the result of all this is quite sad. Certain facts are being continually rediscovered because of such omissions, since the original papers were ignored and then re-ignored. Resentment is engendered in the ignored authors, thereby creating bitterness among scientific workers when there should be friendship.

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An author resents being ignored much more than being disagreed with. This is especially true of foreign authors, who begin to feel that the scientists of a particular country are chauvinistic. But what is much worse, the scientific knowledge embodied in the collection of papers or journals becomes infused with selfish jockeying and human dross which detracts from its objectivity and, hence, immortality as science.

It is the practice of many editors to send controversial papers to the authors being refuted for review. Controversy is thus avoided in the literature simply by this method of disapproval of an opposing viewpoint. The literature thus becomes drier, more restrained and suppressed, instead of being healthy and lively. Everyone in science enjoys a good fight, even the participants, especially if the outcome is the synthesis of a new point of view.

Now, what can or should be done about this situation? The only remedy lies in the hands of editors and the members of editorial boards who review papers for editors. First, the quoted literature should be carefully scrutinized for relevant omissions. It might even be necessary to supply editors and reviewers with a list of pertinent literature for each paper as prepared by a qualified person. The author could then be informed of any pertinent omissions in his bibliography. This would subsequently be an additional factor influencing the decision for or against acceptance of any given paper.

Clinical Communications

The Use of Phenylephrine in the Differentiation of Fallot's Tetralogy From Pulmonary Stenosis With Intact Ventricular Septum

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Previous studies have shown that when severe pulmonary stenosis is combined with a large ventricular septal defect (Fallot's tetralogy), the length and intensity of the systolic murmur are determined both by the severity of the stenosis and the systemic resistance.[1-4] When the septum is intact, however, the murmur's length and intensity are determined by the severity of the stenosis and not directly by the systemic resistance. Thus, abrupt fall in systemic resistance following inhalation of amyl nitrite reduced right ventricular pressure and pulmonary flow and murmur in cases of the tetralogy, but had no such direct influence when the septum was intact.[2,5] In the latter instance the right ventricular pressure and murmur increased in response to the increased volume rate of venous return induced by sudden reduction in peripheral resistance. These observations proved the important role of the septal defect in explaining the different behavior of the systolic murmur in the two conditions.

The purpose of this paper is to study the effect of increasing the systemic resistance in the two conditions. A rise in systemic resistance should increase right ventricular pressure, pulmonary flow and murmur in cases of the tetralogy, but should have no such effect when the septum is intact. Phenylephrine was selected as a suitable pressor agent, since Besterman[6] had described its useful effect in eliciting difficult aortic and mitral murmurs in cases of acute rheumatic fever. The drug aids auscultation by provoking marked bradycardia with an

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increased stroke volume during its hypertensive effect. It was shown to be safe, provided the maximal dose was not exceeded, and this has been confirmed.

The beneficial effect of systemic hypertension on pulmonary blood flow in cases of Fallot's tetralogy was previously shown by Hamilton and associates,[7] and Vogelpoel and Schrire[1] independently reported the favorable combination of coarctation of the aorta and Fallot's tetralogy. These observations were the first to draw our attention to the paramount importance of the systemic resistance in controlling pulmonary blood flow and murmur in the tetralogy. Furthermore, they suggested that pressor agents might be a useful tool in the study of the pulmonary second sound in the tetralogy.[3,4] It will be shown that the increased pulmonary flow and pressure following the administration of phenylephrine is capable of eliciting a previously unrecordable pulmonary second sound even in severe cases of tetralogy.

MATERIAL AND METHODS

There were 10 cases of Fallot's tetralogy and 6 cases of pulmonary stenosis with intact ventricular septum. The diagnosis was proved in all cases by methods previously described.[1-4] It was confirmed at operation in 3 cases of tetralogy and in 5 cases of pulmonary stenosis. By Fallot's tetralogy is meant severe infundibular or valvular stenosis with large ventricular septal defect and ventricular pressures of the same order. Even in acyanotic cases the stenosis is relatively severe, permitting, at most, a small left-to-right shunt (up to 2 liters per minute at rest). Cases of large ventricular septal defect with large left-to-right shunts and mild pulmonary stenosis or small septal defects with mild pulmonary stenosis have been excluded. Such situations, in our view, are not true examples of acyanotic tetralogy.

The severity was graded 1 to 4, according to criteria described fully elsewhere.[3,4] In cases of pulmonary stenosis with intact ventricular septum the stenosis was considered mild when the right ventricular pressure was less than 60, moderate when it was 60-120, severe when it was 120-180, and very severe when it exceeded 180 mm. Hg. The severity of the tetralogy was also graded 1 to 4, corresponding to mild, moderate, severe, extreme, using a clinical method of assessment.

The effects of phenylephrine on the systemic and right ventricular pressure were studied in 9 of the 10 cases of tetralogy and in 5 of the 6 cases of pulmonary stenosis. In the 2 cases not studied at catheterization, the injection was given intravenously and the effect on the blood pressure (cuff method) and phonocardiogram was studied. During routine diagnostic cardiac catheterization a control recording was made of the right ventricular and systemic pressures (brachial and femoral artery), together with a high-frequency phonocardiogram, using the N.E.P. multichannel recording apparatus. Immediately consecutive right ventricular and systemic pressures were recorded through a two-way tap attached to a manometer head. More recently, the pressure tracings were recorded synchronously, using two manometers adjusted to give identical base line and sensitivity. The phonocardiogram was recorded at the *same attenuation* throughout, and frequent recordings at fast paper speed (80 mm. per second) were made during *held expiration*. Between the fast strips, the recordings were made at slow paper speed (2.5 or 8 mm. per second). After having obtained a control recording, we injected phenylephrine slowly via the catheter into the right ventricle. The change in systemic pressure and pulse rate was monitored on an oscilloscope, and continuous recordings were made at slow speed, interspersed with frequent short recordings at fast speed. A response was usually noticeable about 15 seconds after 0.25 mg. of the drug had been injected, and if the response was only slight, another 0.25 mg. was given slowly. Usually, 0.5 mg. was well tolerated, adequate, and effective. The dose was purposely exceeded in 2 cases in order to produce a maximal pressor response. In one case of tetralogy, 1.5 mg. was given, without ill effect or production of ectopic rhythm.

The peak rise in blood-pressure occurred within the first minute; thereafter the pressure gradually returned to the initial level within about 6 to 8 minutes, depending on the dose used

and the individual response. The duration of injection was noted and a signal registered at 7.5-second intervals thereafter. Samples of arterial blood were taken before and during the peak action of the drug in several cyanosed subjects. The injection was occasionally repeated after 15 or more minutes, with the catheter placed in the pulmonary artery so that we could study the effect on the pulmonary arterial pressure.

In most cases, amyl nitrite was administered several minutes after the injection, while the pressures were subsiding, but still high. The technique used was the same as described in previous papers.[2,5]

RESULTS

1. *Fallot's Tetralogy.—*

Effect on the systemic and right ventricular pressures: Data were obtained in 9 patients, as shown in Table I and Figs. 1 and 2. Four were acyanotic at rest, 1 had moderately severe tetralogy, and 4 were severely disabled. In each subject, phenylephrine caused a similar rise in systemic and right ventricular systolic pressures. In 4 patients the systolic pressures before phenylephrine were discrepant (systemic exceeding right ventricular in 2 patients by 18 and 35 mm. Hg, respectively, and right ventricular exceeding systemic in the other 2 by 22 and 25 mm. Hg, respectively), but during the hypertensive and bradycardic response the pressures became virtually identical. The average rise in systemic systolic pressure was 41 mm. Hg (range, 20-98 mm. Hg), whereas the average rise in right ventricular systolic pressure was 41.5 mm. Hg (range, 25-117 mm. Hg). The change in the contour of the systemic pulse wave was always striking, in that two peaks emerged, the first being a striking anacrotic notch or shoulder, followed by a prolonged "tidal" wave.[8] Even more striking was the change in the dicrotic notch, which progressively ascended the descending limb of the pulse wave while the dicrotic wave diminished in amplitude and sometimes disappeared (Figs. 1-3). As the pressor effect wore off, so the anacrotic and tidal wave shoulders became less pronounced, while the dicrotic notch level descended again. The changes presumably resulted from a marked increase in systemic peripheral resistance.[9] There was usually a marked rise in right ventricular end-diastolic pressure.

Bradycardia was always produced, although the degree varied and was not directly proportionate to the rise in blood pressure. Transient nodal rhythm not infrequently occurred. In some subjects, pre-existing premature beats were abolished, whereas in others, phenylephrine caused extrasystoles.

Effect on pulmonary arterial and infundibular chamber pressure: In one case the pulmonary arterial pressure rose from 30/10 to 40/15 mm. Hg, and in another the pressure in the infundibular chamber rose from 20/0 to 60/10 mm. Hg. during the peak action of phenylephrine.

Effect on the arterial oxygen saturation: The effect on arterial oxygen saturation was studied in 3 patients with severe tetralogy who were deeply cyanosed. In all there was a striking increase in oxygen saturation during the peak action of phenylephrine (see Table I and Fig. 1).

Effect on the systolic murmur and heart sounds: Striking intensification of the murmur was shown in all 10 patients. The change in murmur was more dra-

TABLE I. THE EFFECTS OF PHENYLEPHRINE IN CASES OF FALLOT'S TETRALOGY

CASE NO.	PATIENT, AGE, SEX	SEVERITY (1-4)	BEFORE PHENYLEPHRINE					AFTER PHENYLEPHRINE						COMMENT
			SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	PAP (MM. Hg)	ART. O_2 (%)	PHONOCARDIOGRAM	SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	PAP (MM. Hg)	ART. O_2 (%)	PHONOCARDIOGRAM	DOSE OF PHENYLEPHRINE (MG.)	
1.	B.P. 13, M	1	160/75 150/75	— 132/10	30/10 —	95 —	75/min. Loud pan SM goes beyond A_2. Soft P_2 0.09 sec. split	180/105 170/105	— 170/15	40/15 —	— —	65/min. SM much louder, reaches P_2. P_2 little louder, 0.08 sec. after A_2	0.4	Acyanotic, L-R shunt 2 L./min. Infundib. stenosis. Amyl nitrite dropped B.P., RVP. SM softened and shortened, P_2 disappeared
2.	M.K. 26, F	1	100/60	122/5	15/5	97	75/min. Loud SM. Crescendo in midsystole goes beyond A_2. Very soft P_2 0.10 sec. after A_2	170/95	160/15	—	—	56/min. SM, and P_2 much louder, reaches P_2. Split remains 0.10 sec.	0.5	Acyanotic, L-R shunt 2 L./min. Infundib. stenosis. Amyl nitrite caused reverse effect as above (see Fig. 2)
3.	V.S. 13, F	1	100/65	95/5	29/6	94	78/min. Loud SM partially buries A_2. No P_2; mild pulmonary incompetence	130/110	138/20	—	—	55/min. SM much louder, goes beyond A_2. PI murmur much louder. No P_2	0.75	Post-Inf. resection now acyanotic. L-R shunt 2 L./min. Amyl nitrite caused reverse effect as above, and PI murmur disappeared
4.	K.M. 6, M	1	100/60	98/–2	—	95	100/min. Loud SM. A_2 partially buried. Soft P_2, wide split	125/75	125/15	—	—	55/min. SM louder, goes beyond A_2. P_2 much louder. Split unchanged	0.75	Acyanotic. Infundibular stenosis. Amyl nitrite produced reverse effect
5.	Q.B. 2, M	2	92/45	95/8		80	100/min. Loud SM. Crescendo before midsystole; ends well before A_2. No P_2	160/70	165/20	—	—	80/min. SM very loud. Crescendo in late systole, goes beyond A_2. Soft P_2 emerged 0.07 sec. after A_2	0.8	Moderate case. Amyl nitrite caused reverse effect

6.	F.S. 24, F	2	110/70 (cuff)	—	—	—	68/min. Loud SM. Crescendo before midsystole, ends before A_2. No P_2. Slight aortic incompetence	160/120 (cuff)	—	—	—	46/min. SM louder, but crescendo and duration same. AI murmur louder. No P_2	0.4	Moderate case. Amyl nitrite had reverse effect
7.	P.K. 16, M	3	117/75	117/0	1.C. 20/0	69	80/min. Very soft, short, early SM. Loud aortic ejection sound. No P_2	215/120	220/20	1.C. 60/10	81	38/min. Loud SM. Crescendo well before midsystole, but reaches A_2. Ejection sound buried. Soft P_2 0.12 sec. after A_2	1.5	Severe case. Infundib. stenosis. No side effects to large dose. Amyl nitrite caused reverse effect, as above
8.	S.vZ. 3, F	3	80/70	85/5	12/7	53	100/min. Soft, short, early SM. Aortic ejection sound	120/96	120/15	—	73	88/min. SM louder. Crescendo still early but reaches A_2. No P_2. Aortic ejection sound buried	0.5	Severe case. Amyl nitrite caused reverse effect and Art. O_2 dropped to 69
9.	N.vN. 7, F	3	100/70	125/5	—	56	Very soft, short early SM ends in midsystole. Aortic ejection sound. No P_2	150/105	150/10	—	85	SM much louder. Crescendo in midsystole, extends slightly beyond A_2. P_2 emerged 0.08 sec. after A_2	0.5	Severe case. Amyl nitrite caused reverse effect and dropped Art. O_2 (see Fig. 1)
10.	I.F. 22, F	3	135/75	100/0	—	46	160/min. Soft, short SM. Aortic ejection sound	155/95	140/10	—	—	120/min. SM much louder and longer. Aortic click louder	0.5	Reverse effect after amyl nitrite

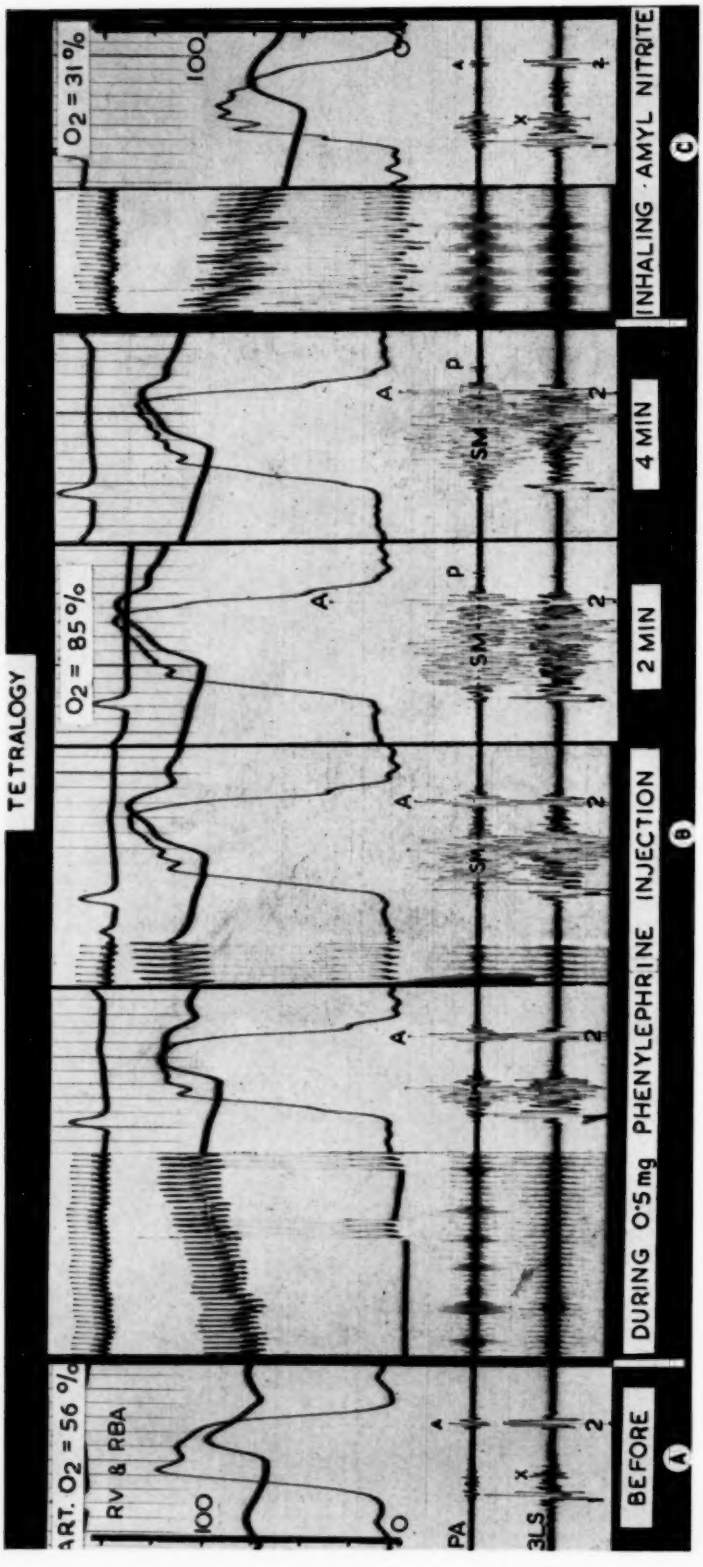

Fig. 1.—*Severe tetralogy.* The effect of increasing and decreasing systemic resistance on the arterial O_2 saturation, right ventricular and systemic pressures, and phonocardiogram. *A*, Before phenylephrine, the very soft, short, early systolic murmur, with aortic ejection sound (*X*) and absent pulmonary component, indicated severe tetralogy with poor pulmonary blood flow. Arterial O_2 saturation was 56 per cent, RV 125/5 and RBA 100/70 mm.Hg. *B*, During injection of phenylephrine, the systemic and RV systolic pressures became identical, both rising steadily together, reaching a peak at 2 min. (RV 150/10; RBA 150/105 mm. Hg). The rise in RV pressure caused progressive improvement in pulmonary blood flow, as shown by the striking change in the murmur. The first response was increased loudness, the murmur remaining very early and short. Thereafter it progressively lengthened, and by 4 min. extended slightly beyond A_2. A soft, delayed (0.08 sec.) pulmonary component (P_2) emerged at 2 min., but only after the murmur lengthening had indicated increased pulmonary flow and arterial O_2 saturation risen to 85 per cent. *C*, At 4 min., when RV and RBA pressures were still high and the phonocardiogram showed good flow, the systemic resistance was abruptly reduced by amyl nitrite. The rapid fall in RV and RBA pressures to 95/2, and 80/52 mm. Hg was shown. Note the pronounced softening and shortening of the murmur and disappearance of P_2, indicating a marked drop in pulmonary flow and pressure. Arterial O_2 saturation fell to 31 per cent.

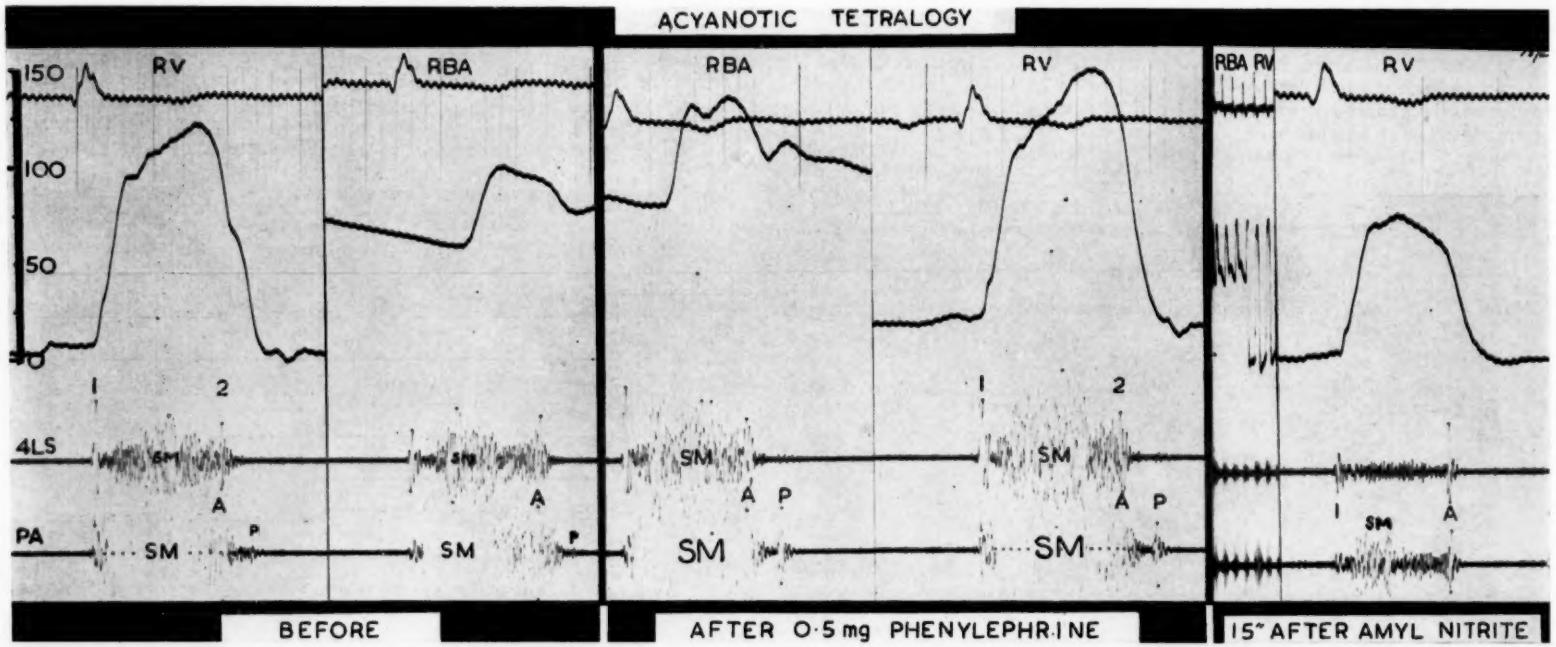

Fig. 2.—*Acyantotic tetralogy.* Effect of increasing and decreasing systemic resistance on the murmur and pulmonary second sound. Note the similar increase in systemic and RV systolic pressures after phenylephrine and decrease after amyl nitrite, thereby proving Fallot's tetralogy. The change in intensity of the murmur and pulmonary component (*P*) with increase and decrease in systemic resistance likewise proved Fallot's tetralogy. The intensification of the very soft and delayed (0.10 sec.) P_2 was striking after phenylephrine, when RVP had risen from 125/5 to 155/10 mm. Hg and systemic from 100/60 to 130/80 mm. Hg. Splitting remained very wide at 0.11 sec., showing no selective delay in aortic valve closure as seen in stenosis with intact septum. Fifteen sec. after amyl nitrite, RV and RBA pressures dropped to 70/0 and 70/30 mm. Hg, respectively, with marked softening of the murmur and disappearance of P_2, suggesting a drop in pulmonary flow and pressure.

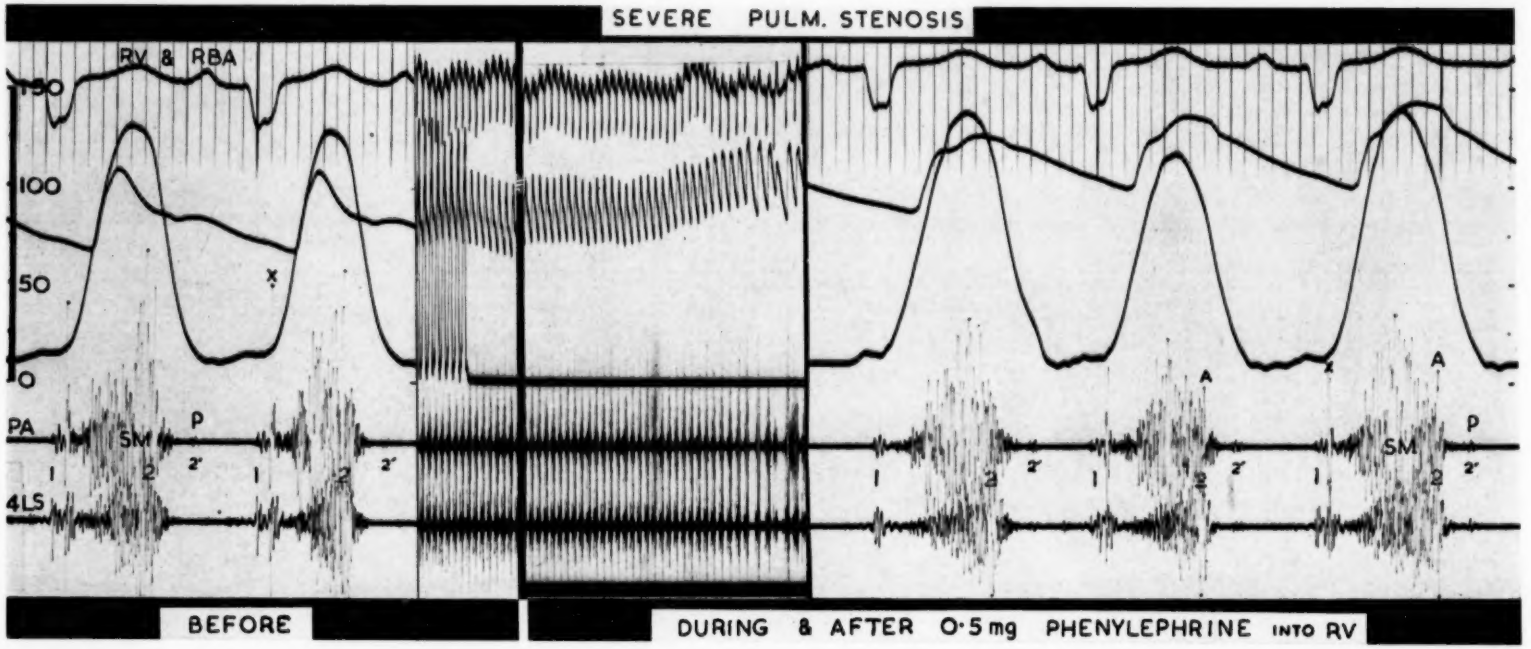

Fig. 3.—*Severe pulmonary stenosis.* The effect of phenylephrine on the phonocardiogram and synchronously recorded right ventricular and brachial arterial pressure tracings. Before the injection the loud, kite-shaped murmur completely engulfed A_2 but ended before the very much delayed and soft P_2, indicating severe stenosis with intact septum. The right ventricular pressure (132/12 mm. Hg) exceeded the systemic pressure (110/68 mm. Hg), suggesting, but not proving, an intact septum. During and after the injection, the systemic pressure rose progressively, with marked change in pulse contour, to 142/100 mm. Hg, behaving independently of the RV pressure, which increased slightly to 140/12 mm. Hg. The three cycles recorded at fast speed followed a ventricular premature beat (not shown) and showed right, but not left, ventricular alternans, during which the systemic and RV systolic pressures were discrepant, suggesting an intact ventricular septum. The murmur softened slightly and the pulmonary component remained soft, whereas the aortic component seemed to shift slightly to the right with each successive systole. The pulmonary ejection sound (*X*) softened slightly. The behavior of the phonocardiogram favored an intact septum (compare with Fig. 2).

matic in the severe cases in which the murmur was initially soft, short, and early. Following the administration of phenylephrine, it became much louder and more prolonged. The progressive intensification and lengthening of the murmur with progressive rise in right ventricular and systemic blood pressure is shown in Fig. 1. In this case the arterial oxygen saturation rose from 56 to 85 per cent, proving that the change in murmur did, in fact, accurately reflect the increased pulmonary blood flow from increased systemic resistance. The emergence of a soft pulmonary second sound 0.08 second after the aortic sound in a tetralogy of this severity was of great interest (see below).

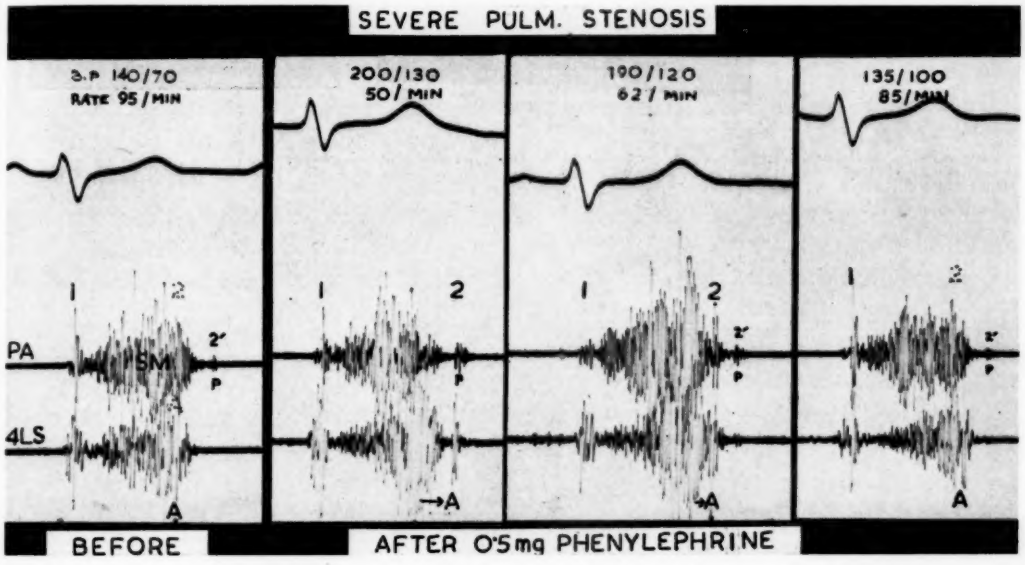

Fig. 4.—*Severe pulmonary stenosis.* Before phenylephrine the phonocardiogram was that of very severe stenosis, the murmur extending well beyond, and burying, the aortic component and ending before the very much delayed (0.11 sec.) and soft pulmonary component (*2,P*). RVP was 195/0 mm. Hg. Despite the profound hypertensive and bradycardic response to 0.5 mg. of phenylephrine intravenously, there was little change in the murmur and pulmonary component, proving that the ventricular septum was intact (compare with Figs. 2 and 5). A striking feature was the marked shift to the right of the aortic second sound from prolongation of left ventricular systole during the rise and peak action of the drug, and its gradual return thereafter. By 6 min. the sound had nearly returned to its former position within the murmur.

Although the murmur became much louder and longer in the severe cases, the site of the crescendo in systole changed much less.

In the 4 acyanotic subjects the murmur was initially very loud and prolonged. Nevertheless, phenylephrine caused a marked intensification and slight, but maximal, prolongation, in that the murmur reached the delayed pulmonary component (Fig. 2).

Phenylephrine intensified both aortic and pulmonary components of the second sound. In 3 acyanotic patients the drug greatly intensified the initially very soft and delayed pulmonary component. The aortic and pulmonary components remained widely separated throughout the hypertensive effect of phenylephrine, suggesting that left ventricular systole had not become selectively

delayed as in some cases of pulmonary stenosis with intact ventricular septum (see below and compare Figs. 2 and 4). Presumably, prolongation of systole from sudden hypertension affects both ventricles equally when pulmonary stenosis is combined with a large ventricular septal defect. Of special interest was the emergence of a soft, delayed pulmonary component in 3 patients with severe tetralogy in whom this sound was previously unrecordable (Table I and Figs. 1 and 5). The sound emerged only after the murmur had first become greatly intensified and lengthened, indicating increased pulmonary flow. This sequence suggested that an increase in pulmonary flow preceded the rise in pulmonary arterial pressure necessary to induce recordable pulmonary valve closure. It is also likely that phenylephrine increased the pulmonary pressure by increasing the pulmonary vascular resistance. In one of the cases the infundibular pressure had risen from 20/0 to 60/10 mm. Hg, and systemic arterial oxygen saturation from 69 to 81 per cent, by the time the pulmonary sound emerged.

The aortic ejection sound recorded in all 4 severe cases became engulfed by the intensified systolic murmur following phenylephrine (Figs. 1 and 5). Since ejection into the pulmonary artery precedes ejection into the aorta, the systolic murmur commences before the aortic ejection sound; hence, when loud, the murmur completely buries the sound. This evolution of events is well shown in Fig. 1.

Effect of amyl nitrite given after phenylephrine: Amyl nitrite was administered to 9 patients in order to reduce abruptly the systemic resistance still elevated by phenylephrine. By this means a rapid and progressive drop in both systemic and right ventricular pressures was induced in all cases during, and for some 30 seconds after, the inhalation (Fig. 1). The murmur softened and shortened, reflecting a pronounced drop in pulmonary flow, and the pulmonary component of the second sound disappeared, indicating a drop in pulmonary arterial pressure. The arterial oxygen saturation dropped sharply in 3 severe cases in which this effect was studied (Table I and Fig. 1).

Amyl nitrite also caused a rapid obliteration of the anacrotic and tidal wave shoulders induced by phenylephrine, as well as a rapid descent of the dicrotic notch and disappearance of the dicrotic wave. These changes in pulse contour presumably indicate a lowered systemic resistance.

2. *Pulmonary Stenosis With Intact Ventricular Septum.*—

Effect on the systemic and right ventricular pressures: Data were obtained in 4 patients, as shown in Table II. Mild stenosis was present in the first subject, moderate stenosis in the second, and severe stenosis in the last two subjects. Phenylephrine caused a rise in systemic pressure, which behaved quite independently of the right ventricular pressure. Thus, the mean rise in systemic systolic pressure was 57 mm. Hg (range, 37-115 mm. Hg), whereas the mean rise in right ventricular systolic pressure was only 4 mm. Hg (range, −9 to 12 mm. Hg). In one severe case the systemic pressure rose from 107/65 to 148/100 mm. Hg, and the right ventricular pressure dropped from 152/0 to 143/0 mm. Hg. Although the systolic pressures became nearly equal by coincidence during the peak hypertensive effect, their unrelated behavior was shown during a short phase of right ventricular alternans induced by ventricular premature beats (Fig. 3). Thus,

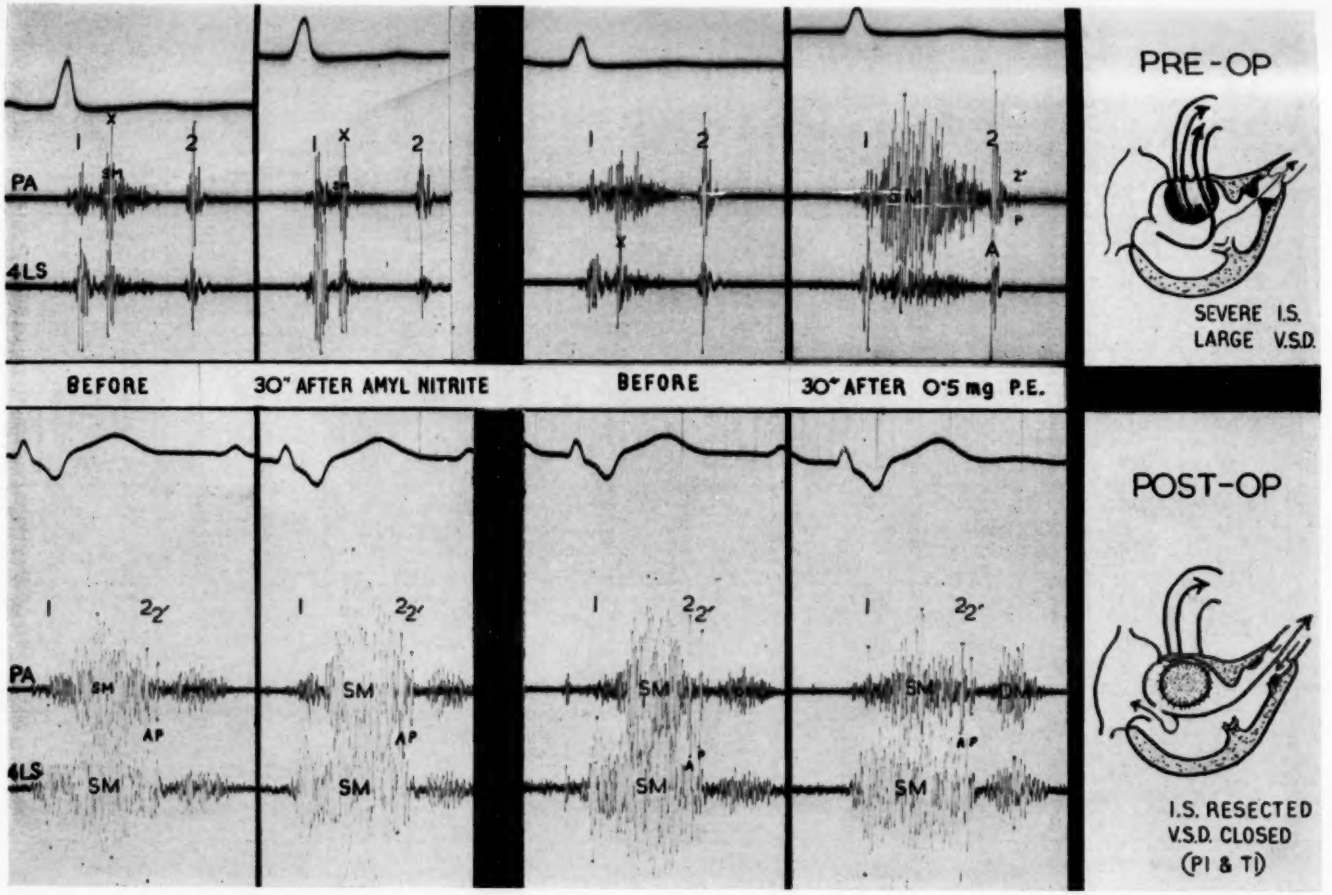

Fig. 5.—*Severe tetralogy before and after repair of large septal defect and infundibular resection.* The study proves that the systemic resistance directly controls pulmonary blood flow and murmur in the tetralogy because of the presence of a large septal defect. Before surgery, decrease and increase in systemic resistance with amyl nitrite and phenylephrine, respectively, caused pronounced decrease and increase in pulmonary flow and murmur. Note emergence of soft, delayed (0.07 sec.) P_2 and loud murmur engulfing aortic ejection sound (*X*) after phenylephrine (B. P. rose from 130/90 to 140/120 mm. Hg). Following surgery which created an intact ventricular septum, similar manipulation of systemic resistance with amyl nitrite and phenylephrine failed to provoke the same change in murmur. The systolic murmur (*SM*) (pulmonary ejection systolic murmur in *PA*, and probably tricuspid regurgitant systolic murmur in *4LS*) increased after amyl nitrite but did not change after phenylephrine. Note appearance of normal P_2 and close splitting after surgery, suggesting a rise in pulmonary arterial pressure to normal and adequate relief of stenosis, respectively. The diastolic murmur (*DM*) following P_2 was due to pulmonary incompetence.

TABLE II. THE EFFECT OF PHENYLEPHRINE IN CASES OF PULMONARY STENOSIS WITH INTACT SEPTUM

CASE NO.	PATIENT, AGE, SEX	SEVERITY (1-4)	BEFORE PHENYLEPHRINE					AFTER PHENYLEPHRINE						COMMENT
			SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	PAP (MM. Hg)	ART. O_2 (%)	PHONOCARDIOGRAM	SYSTEMIC B.P. (MM. Hg)	RVP (MM. Hg)	PAP (MM. Hg)	ART. O_2 (%)	PHONOCARDIOGRAM	DOSE OF PHENYLEPHRINE (MG.)	
1.	J.P. 17, F	1	108/50	40/0	17/5	96	105/min. Short SM. Crescendo before midsystole ends at A_2. Split 0.06 sec.	150/75	—	27/9	—	52/min. Slight increase in loudness but not length. Split closed due to delay in A_2	0.5	Amyl nitrite caused gross intensification
2.	L.M. 8, M	1	100/65	35/2	22/6	—	85/min. Short midsystole SM. No P_2. Slight pulmonary incompetence	215/115	44/10	—	—	65/min. No change in SM. PI murmur much louder	0.4	1 year postvalvulotomy. P_2 absent. Mild PI
3.	E.H. 6, M	2	150/65 140/85	— 70/0	10/6 —	96 —	110/min. Loud SM. A_2 partially buried. Split 0.06 sec. Pulmonary ejection click	175/100 175/102	— 75/–5	25/15 —	— —	80/min. SM slightly softer and split closed. Ejection sound louder	0.3	—
4.	F.W. 10, M	3	107/65	130/12	16/6	97	108/min. Loud SM. Very late crescendo. A_2 buried. Very soft P_2. Loud pulmonary click	148/100	142/10	—	94	82/min. SM slightly softer. Split remains 0.08 sec. Pulmonary click little softer	0.5	No significant change in SM or split (see Fig. 3)
5.	M.M. 7, M	3	98/65	152/0	25/10	96	105/min. Loud SM. Late crescendo A_2 buried. Very soft P_2 0.08 sec. Loud pulmonary click	135/90	143/0	—	95	60/min. SM unchanged. Click disappeared. Split narrowed to 0.06 sec.	0.75	During nodal rhythm after P.E., SM much softer and shorter despite high RVP
6.	W.vD. 10, M	4	140/70 (cuff)	195/0	—	—	95/min. Loud, long SM. A_2 buried. Split 0.11 sec.	200/130 (cuff)	—	—	—	50/min. SM virtually unchanged. A_2 very much delayed, closing split completely. P_2 slightly increased	0.5	Severe B.P. response may explain grossly delayed A_2 closure (see Fig. 4)

the systolic pressure of the weaker right ventricular systole fell well below the systemic pressure which showed no evidence of left ventricular alternans.

In the very severe case in which catheterization was not done the systemic pressure rose from 140/70 to 200/130 mm. Hg.

The effect of phenylephrine on the contour of the systemic pulse wave was the same as described above.

Effect on the pulmonary arterial pressure: Data were obtained in 2 subjects. The pulmonary arterial pressure rose from 17/5 to 27/9 mm. Hg (systemic pressure rising from 108/50 to 150/75 mm. Hg) in the first subject, who had mild stenosis; and from 10/6 to 25/15 mm. Hg (systemic rising from 150/65 to 175/100 mm. Hg) in the second, who had moderate stenosis.

Effect on the arterial oxygen saturation: The effect on the arterial oxygen saturation was studied in the 2 severe cases; the saturation dropped from 97 to 94 per cent in one, and from 96 to 95 per cent in the other. The changes were clearly of no significance.

Effect on the systolic murmur and heart sounds: Six patients were studied; the stenosis was mild in 2, moderate in 1, severe in 2, and very severe in 1 (Table II). The change in intensity and length of the murmur was insignificant, but one must bear in mind the marked bradycardia and increased stroke volume caused thereby. This probably accounted for the slightly increased intensity of the murmur in 3 patients. In 2 patients the murmur actually became a little softer, despite the slight rise in right ventricular pressure.

Comparison of Figs. 1 and 2 with 3 and 4 at once illustrates that a rise in systemic resistance does not significantly change a pulmonary stenotic murmur when the ventricular septum is intact. This is also shown in a patient with tetralogy who was studied before and after closure of the septal defect (Fig. 5). Before surgery, phenylephrine greatly intensified and lengthened the murmur and elicited a pulmonary second sound. That this effect was due to the large septal defect was shown by failure of phenylephrine to cause a change in the murmur and pulmonary second sound when the defect was closed and the stenosis resected. Similarly, the decrease in the murmur after amyl nitrite prior to surgery was also shown to be dependent on the presence of a large septal defect.

The effect on the second heart sound differed from that in the tetralogy. In 3 cases during the early hypertensive effect of phenylephrine, splitting of the second sound disappeared because of marked delay (shift to the right) in aortic valve closure, presumably from prolongation of left ventricular systole. In the first patient with mild stenosis, the split was 0.06 second before phenylephrine, but during the rising systemic pressure the second sound became single and remained thus for 3 minutes; thereafter the aortic sound gradually returned to its former position, with gradual increase in the width of splitting. In the second patient with moderate stenosis, a split of 0.06 second was closed by marked delay in aortic valve closure. In the third patient with very severe stenosis, pulmonary valve closure was delayed 0.11 second because of grossly prolonged right ventricular systole. During the severe hypertensive response to phenylephrine (B.P. rose from 140/70 to 200/130 mm. Hg) the aortic sound appeared to shift to the right; thereafter it slowly moved back to its former position within

the crescendo of the murmur (Fig. 4). In the remaining 3 cases, splitting narrowed slightly in one but not in the other, and in the third, splitting was absent because of an unrecordable pulmonary component.

There was little change in the intensity of the pulmonary second sound in comparison to its relatively marked increase in the tetralogy, suggesting that pulmonary blood flow and pressure are much less influenced by the systemic resistance when the ventricular septum is intact.

In 2 patients having severe stenosis with loud pulmonary ejection sounds, the sound became softer in one and disappeared in the other after phenylephrine. However, in a patient with moderate stenosis the pulmonary ejection sound became louder.

Effect of amyl nitrite given after phenylephrine: In all 5 patients, amyl nitrite resulted in a prompt fall in systemic pressure, whereas the right ventricular pressure and murmur steadily increased 30 to 45 seconds after amyl nitrite was withdrawn, reflecting the dynamics of pulmonary stenosis with intact ventricular septum.[2,5]

DISCUSSION

The strikingly different response of the right ventricular pressure and systolic murmur to increasing systemic peripheral resistance in the two conditions is attributed to the presence of a large ventricular septal defect in the tetralogy. The findings confirmed previous observations[1-4] that in the tetralogy, pulmonary blood flow, and hence murmur, is determined both by the severity of the stenosis and the systemic resistance. An increase in the latter resulted in elevation of both systemic and right ventricular pressures. The improved pressure gradient across the pulmonary or infundibular stenosis resulted in ejection of a greater volume of blood through the stenosis, as reflected by the intensification and lengthening of the murmur and the increase in arterial oxygen saturation. The greater the rise in right ventricular pressure, the greater the improvement in pulmonary blood flow. Even in severe cases, marked transformation of the murmur could be produced with emergence of a previously unrecordable pulmonary second sound.

The important role of the systemic resistance in governing pulmonary blood flow in the tetralogy was conclusively shown by the abrupt reversal of the beneficial effects of raised systemic resistance when the resistance was suddenly reduced by amyl nitrite. Thus, the systemic and right ventricular pressures, arterial oxygen saturation, and length and intensity of the murmur rapidly diminished with disappearance of the pulmonary second sound, suggesting marked fall-off in pulmonary blood flow and pressure (Fig. 1.) When the septal defect was closed by surgery in the cases of tetralogy, increase and decrease in systemic resistance no longer produced the same effect (Fig. 5).

In the cases of pulmonary stenosis with intact ventricular septum, increase in systemic resistance caused a rise in systemic blood pressure independently of the right ventricle; hence there was no significant change in the murmur and pulmonary second sound. Selective prolongation of left ventricular systole

causing delayed closure of the aortic valve during the early hypertensive response greatly shortened, or closed, the previously widely split second sound. Narrowing of the split did not occur in the cases of tetralogy, presumably because systemic hypertension would delay systole in both ventricles equally.

The observations on the pulmonary second sound in cases of the tetralogy were of great interest. Phenylephrine elicited soft pulmonary components in 3 severe cases by increasing pulmonary blood flow and pressure sufficiently to make a silent sound recordable. The sound thus rendered recordable was as much delayed (0.07, 0.08, and 0.12 second) as in mild cases, supporting the view that splitting of the second sound is always wide in cases of the tetralogy.[1,3,4] Phenylephrine proved to be useful in identifying a doubtful, delayed, very soft sound as the pulmonary component. In mild cases of tetralogy, when the pulmonary component is just recordable, it is often fleeting because of variation with respiration.[3,4] However, phenylephrine intensified the sound, making its recognition much more certain.

COMMENT

The diagnostic value of phenylephrine is obvious, although as a bedside test it is much less attractive than amyl nitrite. The need for intravenous injection is a major drawback. However, it is very simple to use during cardiac catheterization, and less disturbing than amyl nitrite, while offering a useful means of deciding whether or not a large septal defect accompanies pulmonary stenosis. This is especially true in cases in which the right ventricular and systemic systolic pressures are unequal. Manipulation of the systemic resistance by first increasing it with phenylephrine and then abruptly reducing it with amyl nitrite provides valuable information about the state of the ventricular septum in the difficult case.

It is conceivable that the response to phenylephrine may help in selecting the type of operation for a severe case of tetralogy. A favorable situation would be one in which a moderate rise in systemic resistance is capable of producing a pronounced increase in the length and intensity of the murmur, a rise in oxygen saturation, and a recordable pulmonary component. In 2 of our severe cases in which this occurred, the defects were successfully corrected by a one-stage operation. A less favorable situation would be revealed by failure to induce much lengthening of the murmur and a rise in arterial oxygen saturation despite a marked rise in systemic resistance. This aspect is receiving further study.

Phenylephrine may be of value in assessing whether a residual systolic murmur after complete repair of the tetralogy is due to turbulent ejection of blood through a roughened or stenosed outflow tract as opposed to leak through an incompletely repaired septal defect[4,10] (Fig. 5). When the septum is intact, phenylephrine should produce no significant change; however, in the presence of a ventricular septal defect, marked intensification would be anticipated, since we have shown elsewhere[11] that the murmur of a small and moderate ventricular septal defect is usually greatly intensified when the systolic gradient between left and right ventricles is increased by phenylephrine.

SUMMARY

1. The effect of phenylephrine on the systemic, right ventricular, and pulmonary arterial pressures and on the systolic murmur and heart sounds has been studied in patients with Fallot's tetralogy and pulmonary stenosis with intact ventricular septum.

2. In both conditions, phenylephrine caused a pronounced elevation in systemic blood pressure and bradycardia, depending on the dose given and the individual response. The change in the contour of the pulse wave suggested a marked increase in peripheral systemic resistance.

3. In cases of Fallot's tetralogy, whether severe or acyanotic, the systemic and right ventricular systolic pressures behaved in identical fashion, both rising and falling together. The elevated right ventricular pressure and pressure gradient across the stenosis caused increased pulmonary blood flow and pressure, as reflected by marked intensification and lengthening of the murmur, and intensification of the pulmonary second sound, respectively. The arterial oxygen saturation greatly improved in the cyanosed patients. Amyl nitrite reversed the beneficial effects by abruptly reducing the high systemic resistance.

4. In cases of pulmonary stenosis with intact ventricular septum, whether mild or severe, the systemic and right ventricular pressures behaved quite independently of one another. The change in right ventricular pressure was insignificant, as reflected by insignificant change in the intensity and length of the murmur, allowing for the increased stroke volume from bradycardia. When the hypertensive response was marked, left ventricular systole appeared to be selectively delayed, as judged by marked delay in aortic valve closure, closing a previously widely split second sound.

5. The different behavior of the right ventricular pressure and systolic murmur was attributed to the presence of a large ventricular septal defect. This was proved in a case of tetralogy studied before and after complete repair of the septal defect.

6. The observations support the thesis that pulmonary blood flow, and hence the length and intensity of the murmur, in cases of tetralogy is determined both by the systemic resistance and the severity of the stenosis.

7. Phenylephrine was shown to be a useful tool in studying the pulmonary second sound in cases of tetralogy. By increasing pulmonary blood flow and pressure, this drug greatly intensified the very soft, fleeting, pulmonary component in cases of mild tetralogy, thereby assisting in its recognition. It was also capable of eliciting a pulmonary component in severe cases of tetralogy.

8. The diagnostic value of phenylephrine is described and its possible aid in selecting the operative procedure for severe tetralogy is discussed.

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Reversed Reciprocating Paroxysmal Tachycardia and Its Relationship to the Wolff-Parkinson-White Syndrome

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In 1913, Mines[1] described an arrhythmia of alternating atrial and ventricular contractions which resulted from the application of an appropriate electrical stimulus to the hearts of the frog and rayfish. He ascribed this arrhythmia to refractoriness of part of the A-V conducting system. The atrial stimulus first traveled through the nonrefractory pathway of the A-V node and stimulated the ventricles. The refractory pathway in the A-V node then had sufficient time to recover and was thus able to transmit the impulse in the reverse direction, i.e., back to the atria. Mines termed this arrhythmia *reciprocating rhythm.*

In 1915, White[2] described a basic nodal rhythm in which occasional ventricular bigemini were due to a nodal P wave "sandwiched" between a pair of QRS complexes. He postulated that this represents alternate stimulation of the atria and ventricles occurring during A-V nodal rhythm, when retrograde conduction to the atria is slower than anterograde conduction to the ventricles. The stimulus thus reaches the atria after the conduction fibers have completely recovered, and the activation wave may then return to the ventricles, causing a further ventricular contraction.

Other early reports of this arrhythmia were those of Gallavardin and Gravier[3] and Drury.[4] Dock[5] termed the nonrepetitive form of this arrhythmia *reciprocal rhythm*, thus separating it from the continuous *reciprocating rhythm* of Mines.

Further reports of reciprocal rhythm have not been frequent. Decherd and Ruskin,[6] in 1943, reviewed 22 cases and described an additional 3 cases. Bix,[7] in 1951, found 30 cases and added 4 further examples of his own. Most cases were associated with A-V nodal rhythm. There have also been reports of a reciprocal mechanism resulting in retrograde conduction of extrasystolic and idioventricular beats.[18,19]

First degree retrograde block is necessary for the production of reciprocal rhythm because this delay is required for the atrial impulse to return to the A-V node outside its refractory period.

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Another form of reciprocal rhythm may occur in the presence of a sinus or atrial pacemaker. In this condition the atrial stimulus travels to the A-V node and thence to both the ventricles and atria, producing a P-QRS-P′ "sandwich." The second P wave, owing to retrograde conduction, has a contour differing from that of the first. Katz and Pick[8] have coined the term *reversed reciprocal rhythm* for this mechanism.

Reversed reciprocal rhythm is extremely rare. Only 12 clinical examples have been reported.[6-17] Wolferth and McMillan,[9] in 1929, first described this arrhythmia. The basic rhythm in their case was a 2:1 heart block. They emphasized the late occurrence of the retrograde P wave and believed that this was necessary to allow for recovery of the junctional tissues. Furthermore, the occurrence of the retrograde P wave at about the time of the anticipated sinus P wave suggests that the retrograde P wave either discharges or blocks the formation of the sinus P wave.

Naim,[10] in 1945, described an arrhythmia associated with paroxysmal tachycardia. In the intervals between the attacks of tachycardia it was noted that a normal sinus P wave preceded a QRS complex, which was then followed by a negative P wave. The return of the retrograde atrial stimulus to the ventricles was mostly blocked but could at times provoke a further ventricular contraction. This cycle, when perpetuated, produced a paroxysmal tachycardia of about 140 beats per minute. An example of reversed reciprocating paroxysmal tachycardia is also seen in a case described by Bix.[7]

In 1950, Codina-Altés and Pijoan de Beristain[11] described a case with short paroxysms of tachycardia due to a reversed reciprocating rhythm and suggested that this mechanism was due to the existence of an anomalous A-V communication, probably congenital in origin, capable of conducting impulses in a retrograde manner.

Moe and his co-workers[22] experimentally produced reversed stimulation of the atria following a sinus impulse. They, too, support the concept of a dual pathway to explain this arrhythmia.

Decherd and Ruskin,[6] in 1943, encountered a patient (their Case 3) with reversed reciprocal rhythm showing double atrial stimulation. The first retrograde P wave was the result of rapid retrograde conduction to the atria, and the second, with a longer R-P interval, gave rise to a further ventricular contraction. A similar case was described by Zakopoulos.[12]

A further example of reversed reciprocal rhythm is presented in this report. The arrhythmia caused the patient to have prolonged attacks of paroxysmal tachycardia which were sensitive to changes in posture and vagal stimulation. These maneuvers caused interesting patterns of group beating. A relationship between reversed reciprocal rhythm and the Wolff-Parkinson-White syndrome is postulated.

CASE REPORT

A 21-year-old Eurafrican male complained of spontaneous attacks of palpitations of abrupt onset, equally abrupt termination, and a duration ranging from a few seconds to many hours. These attacks first commenced 3 years previously while he was convalescing from an attack of

malaria. They were relatively infrequent during the first 2 years, occurring about twice weekly. During the last year, however, the attacks were almost continuous, with only occasional remissions. He was not incapacitated by the attacks, and his only symptoms were an awareness of the rapid heart action and slight epigastric discomfort. There was no significant loss in weight, increase in appetite, intolerance to hot weather, or any other indication of hyperthyroidism. There were no further attacks of malaria. His parents were well. There were no siblings.

Examination revealed a well-nourished, rather thin, placid individual in no obvious discomfort. There was no evidence of anxiety, tremor, or excessive perspiration. There was a uniform enlargement of the thyroid gland. The pulse rate when he was in the standing position was 140 per minute and was uninfluenced by respiration, emotion, or exercise. When he was supine, the pulse beats occasionally occurred in short rapid paroxysms of a few seconds' duration, with abrupt start and termination. The remainder of the physical examination was negative.

Investigations.—Erythrocyte sedimentation rate (Westergren), 12 mm. per hour; basal metabolic rate, minus 3; serum protein bound iodine, 3.8 micrograms per 100 ml.; *radioactive iodine uptake, 79.5 per cent;* viral and typhoid agglutinations, negative; modified Coombs test for Brucellosis, negative; serum cholesterol, 300 mg. per 100 ml. Radiologic examination of the chest was normal.

Comment.—There was no clinical evidence of hyperthyroidism. The high radioactive iodine uptake associated with the low serum protein bound iodine indicates the avid thyroid commonly found in persons from an iodine-deficient region in which goiter is endemic.

ELECTROCARDIOGRAPHY

The beginning of the upper strip of Fig. 1 illustrates the termination of an attack of supraventricular tachycardia. Each QRS complex during the attack is followed by a tall, spiked P wave. This supraventricular tachycardia may be interpreted as either a nodal tachycardia with late retrograde conduction of the nodal impulse to the atrium (R-P interval of 0.17 sec.), or an atrial tachycardia with first degree A-V block (P-R interval of 0.28 sec.). Eyeball compression applied during the interval indicated by the arrows terminated the attack. Similar termination occurred with carotid sinus compression and the Valsalva and Müller maneuvers. There follows a period of sinus standstill of 3.2 sec. Recommencement of activity reveals a P wave with a contour different from that seen during the attack of tachycardia. The impulse from this P wave is conducted to the ventricles at P-R interval of 0.24 sec. The QRS complex so recorded does not differ from that recorded during the attack of tachycardia. This QRS complex is also followed by a P wave similar in configuration to that in the paroxysmal tachycardia, and at an R-P interval of 0.17 sec. This P-QRS-P′ pattern represents forward conduction of the sinus impulse to the ventricles, with first degree A-V block and a return of the impulse to the atrium in a retrograde direction. The return of the sinus impulse is the reverse of the usual form of reciprocal rhythm, and is thus a *reversed reciprocal rhythm.* One second later this pattern is again repeated, this time initiating a further attack of paroxysmal tachycardia of about 3 seconds' duration. Following this, there are several short paroxysms of tachycardia, each about 1.8 sec. in duration. Each paroxysm commences with a P wave similar to a sinus P wave and different in contour from the ensuing retrograde P waves. The attack then continued without interruption.

A detailed analysis of these paroxysms is illustrated in Fig. 2. Commencing with a sinus P wave, the impulse is conducted with a P-R interval of 0.22 sec. and records QRS complex 1. The impulse returns from the A-V node to record

a retrograde P wave at an R-P interval of 0.12 sec. This impulse returns once again anterogradely to the ventricles (P-R interval of 0.41 sec.) to record the QRS complex with aberrant contour—QRS complex 2. The impulse returns again from the A-V node to record a retrograde P wave (seen just after QRS complex 2), further returning anterogradely (P-R interval of 0.28 sec.) to record the slightly less aberrant QRS complex 3. In a like manner, a further retrograde P wave is recorded after QRS complex 3, after which the impulse returns to record the normal contour of QRS complex 4. This pattern is repetitive, with

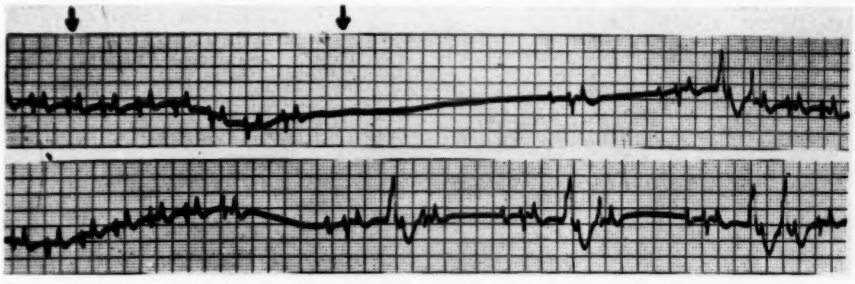

Fig. 1.—Electrocardiogram (Lead V_1, continuous strip) showing termination of an attack of paroxysmal tachycardia by eyeball compression (applied in the interval indicated between arrows), and further paroxysms of reversed reciprocating tachycardia. (See text.)

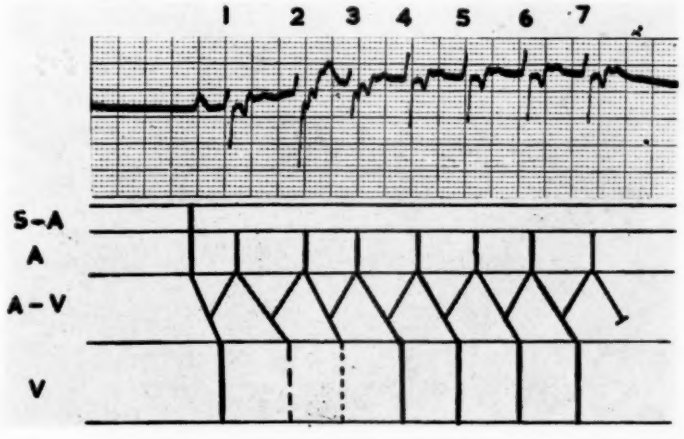

Fig. 2.—Analysis of electrocardiogram (Standard Lead II) showing paroxysm of reversed reciprocating tachycardia. (See text.)

the impulse returning to the atria from the A-V node and then back again to the A-V node and ventricles; the anterograde conduction demonstrates a first degree A-V block (P-R interval of 0.28 sec.). The return of the impulse following complex 7 is blocked, thus terminating the paroxysm of tachycardia. This arrhythmia is therefore a *reversed reciprocating paroxysmal tachycardia.*

The refractory periods of the A-V node and the bundle branches depend *inter alia* on the duration of the preceding cycle length; the longer the cycle length, the longer the refractory period, and vice versa. Slight differences in

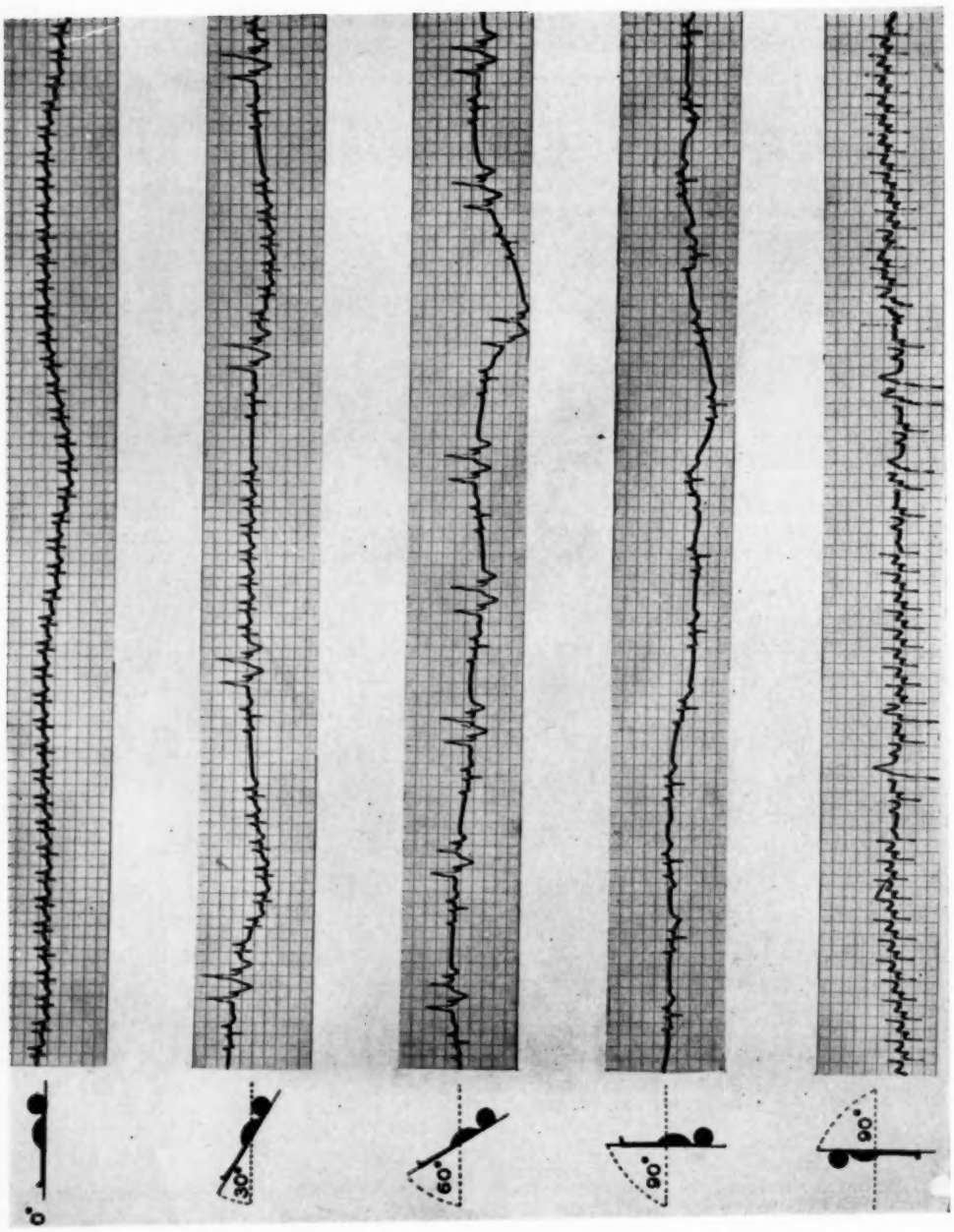

Fig. 3.—Electrocardiogram showing the effects of tilting. Upper four strips, Lead V_1. Lower strip, Standard Lead II.

the refractory periods of the bundle branches, and varying preceding R-R intervals account for the aberrant ventricular conduction resulting in complexes 2 and 3. Thus, the long R-R interval preceding QRS complex 1 allows for recovery of one bundle branch only at the time of anterograde return to the A-V node.

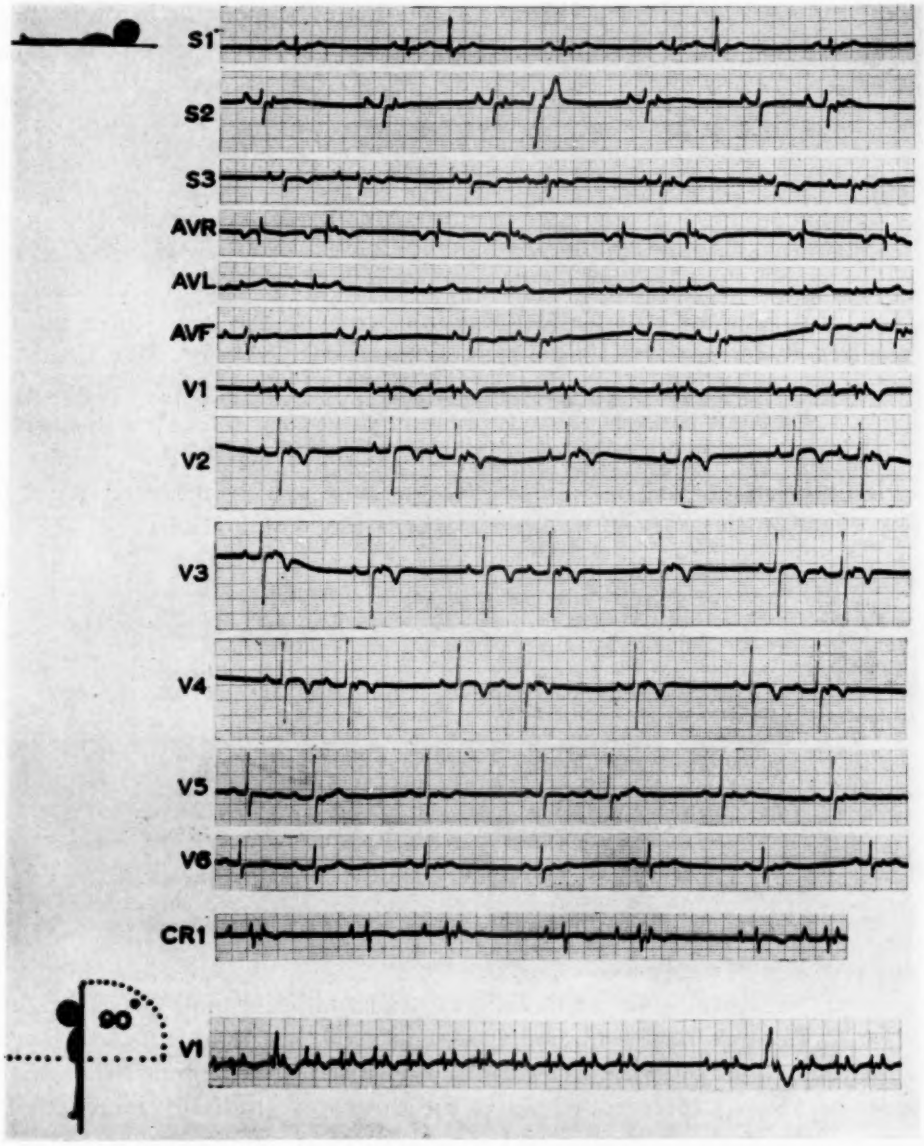

Fig. 4.—Electrocardiogram (all leads) showing grouping of reciprocal and nonreciprocal beats. (See text.)

The shorter R-R interval between complexes 1 and 2 permits a more complete recovery of both bundle branches at the time of the returning atrial impulse and results in a near-normal QRS complex 3. The still shorter interval between complexes 2 and 3 allows for complete recovery of the whole conducting system

at the time of return of the atrial impulse, resulting in the normal QRS complex 4. Short cycle lengths are now maintained, resulting in normal QRS complexes for the remainder of the paroxysm (Figs. 1 to 4). On a similar basis, differences in refractoriness of the A-V node as a result of varying preceding R-R intervals account for the long P-R interval of complex 2.

With the aid of a tilting radiologic table, the effects of posture were noted (Fig. 3). These tests were conducted before the patient had received medication. When the patient was in the standing and horizontal positions, the paroxysms were continuous, with few remissions. When he was tilted head-downward at 60 degrees from the horizontal, the paroxysms were of approximately 1½ seconds' duration. When he was tilted head-downward at 90 degrees from the horizontal, the paroxysms stopped completely; the beats, however, still showed the retrograde return of the sinus impulse to the atria, but return anterograde conduction was now blocked. These postural effects were probably due to the increased venous return from the trunk and lower limbs during the head-down position. This resulted in increased diastolic stretch and stroke volume. The stroke volume, with cardiac acceleration, increased progressively during the first few beats. The increased output caused a rise in pressure in the aorta and carotid arteries, which resulted in reflex slowing via the carotid and aortic reflexes.

It is noteworthy that none of these maneuvers which increased vagal tone had any effect on the R-P intervals, viz., retrograde conduction.

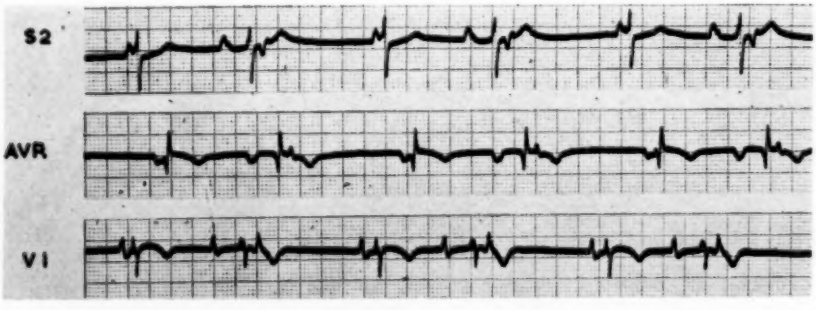

Fig. 5.—Electrocardiograms showing bigeminal pattern of escape and reciprocal beats. (See text.)

Progress.—Digitalis, in normal doses, and quinidine had no effect on the arrhythmia. Because of the obvious sensitivity of this arrhythmia to increases in vagal tone, therapy with Prostigmin was instituted. Commencing with an oral dose of 15 mg. three times daily, the dose was gradually increased to 45 mg. three times daily. The effects of this therapy are illustrated in Fig. 4. The paroxysms are not evident when the patient is lying flat. The arrhythmia now consists of various reciprocal and nonreciprocal beats, usually grouped in pairs. The group beating is in the form of a Wenckebach sequence, commencing with a P-R interval of 0.20 sec. which does *not* result in reciprocal return to the atria, followed by a QRS complex with a longer P-R interval of 0.28 sec. which always results in retrograde return to the atria. The retrograde return of this impulse to the atria discharges the next sinus impulse and thus ends the sequence of con-

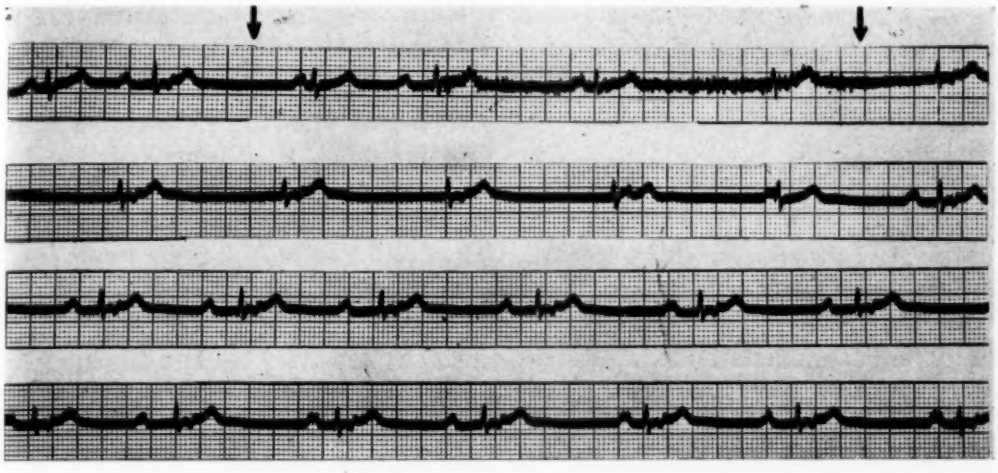

Fig. 6.—Electrocardiogram (Standard Lead II, continuous strip) recorded during a period of digitalis intoxication. Eyeball compression (applied in the interval indicated by arrows) results in depression of the sinus pacemaker, followed by nodal rhythm with retrograde P waves whose contours are identical to those of reciprocal beats and at the same R-P interval. The sequence shown in the second strip illustrates a well-recognized transition from A-V nodal rhythm with late retrograde conduction through atrial fusion and A-V dissociation to sinus rhythm (Bix and Marriott[21]).

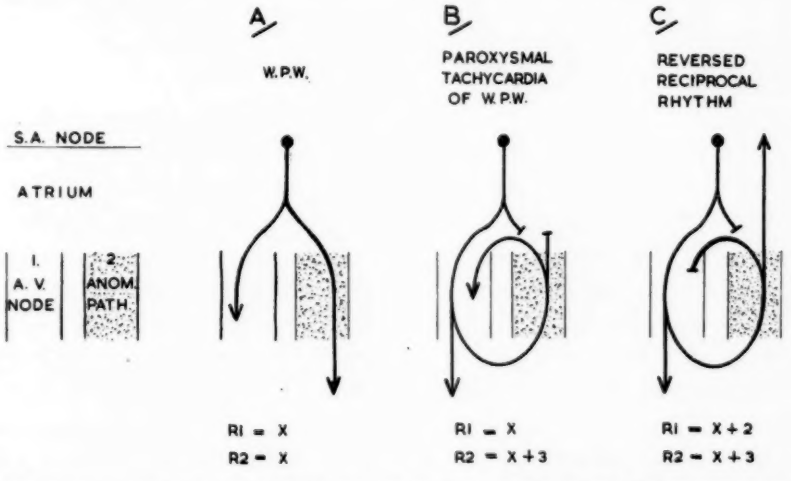

Fig. 7.—Diagrammatic illustration of conduction in the patterns of the WPW syndrome (*A* and *B*), and reversed reciprocal rhythm (*C*). *1*, Normal pathway. *2*, Anomalous pathway. *R*, Refractory period. (See text.)

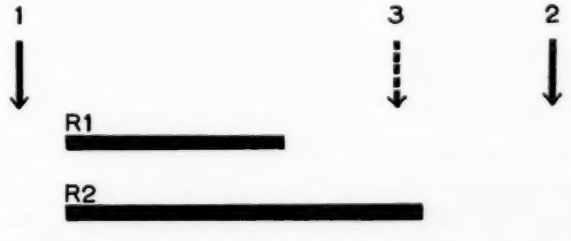

Fig. 8.—Diagrammatic illustration of the effect of atrial impulse frequency on the refractory ratio. *R1*, Refractory period of the normal pathway. *R2*, Refractory period of the anomalous pathway. *1* and *2* illustrate atrial frequency with relative bradycardia; *1* and *3* illustrate atrial frequency with relative tachycardia. (See text.)

ducted beats. Return to the standing position results in short paroxysms of tachycardia similar to that noted in Fig. 3 when the patient was tilted 30 degrees head-downward from the horizontal.

The dosage of Prostigmin was further increased to 60 mg. three times daily. The effects of this increased dosage are illustrated in Fig. 5. The basic rhythm reveals another pattern of bigeminal grouping of the QRS complexes. The first complex is a nodal escape beat. The following sinus impulse is conducted to the ventricles at a P-R interval of 0.26 sec. and is followed by a retrograde impulse. The two complexes constitute a bigeminus with an R-R interval of 1.03 sec. Following a pause (R-R interval of 1.26 sec.) the pattern repeats itself. When the patient assumed the standing position, the paroxysms were again precipitated, but now for only a short period (15 to 16 sec.), following which there was a return to the basic bigeminal rhythm described above.

The question poses itself whether the inverted P waves are not, in fact, atrial premature beats. Two prominent features in this study negate this possibility. First, the abnormal P waves are linked only to those conducted beats which have a prolonged P-R interval. This selective linkage would be extremely fortuitous for atrial premature beats. Secondly, depression of the sinus pacemaker as a result of eyeball compression (Fig. 6) results in nodal beats with late retrograde conduction to the atria, with R-P intervals and P′ wave configuration identical with those of the reciprocal beats.

DISCUSSION

The rarity of reversed reciprocal rhythm is due to the normal, relatively long refractory phase of the A-V junctional tissues, so that any impulse returning from the ventricles finds the A-V node refractory. Retrograde return of a sinus, nodal, or ventricular impulse could occur, however, if a functional longitudinal dissociation of the A-V node existed,[20] so that some of its fibers are left undischarged by the initial forward activation wave, and retrograde conduction through the unused pathway then becomes possible. An analogous situation would be the existence of an anomalous atrioventricular conduction pathway (in addition to the normal pathway) which permitted rapid retrograde conduction. Such a pathway was suggested by Codina-Altés and Pijoan de Beristain[11] and Eldridge[17] as the possible cause for reversed reciprocal rhythm. Furthermore, it has been postulated that this anomalous pathway, although conducting impulses extremely rapidly, has a very long refractory period. This is in contrast to the normal pathway whose rate of transmission of impulses is slower and whose refractory period is short. An atrial impulse arriving at the A-V junction may thus find the normal pathway nonrefractory and the anomalous pathway refractory. The stimulus is then conducted down the normal pathway and returns via the anomalous pathway, thus demonstrating a degree of unidirectional block in the anomalous pathway due to its long refractory phase. The rapidly returning retrograde impulse through the anomalous pathway would, however, still find the atria refractory following their stimulation by the anterograde sinus impulse. Therefore, a further requisite for successful retrograde stimulation of the atria

would be a degree of anterograde and/or retrograde A-V block of sufficient duration to permit recovery of the atria before the arrival of the retrograde stimulus.

To summarize, the three basic requirements for reversed reciprocal rhythm are: (1) an anomalous pathway, (2) unidirectional block in the anomalous pathway due to its long refractory phase, and (3) a degree of block in the A-V junctional tissues.

In Fig. 8 an attempt is made to illustrate graphically the possible forms of conduction in arrhythmias associated with an anomalous pathway. In the illustration the lengths of the refractory periods of the normal (R1) and anomalous (R2) pathways range from a hypothetical quantum X to a maximum of X + 3. These quanta do not represent absolute values but are used as a means of establishing a ratio between the refractory periods of the two pathways, the *refractory ratio.*

The mechanism of conduction in a reversed reciprocal beat is illustrated in Diagram C of Fig. 7. The refractory ratio is R1 = X + 2; R2 = X + 3. The sinus impulse arriving at the atrionodal junction finds the anomalous pathway refractory and is conducted with a degree of A-V block to the ventricles. This impulse returns in a retrograde direction through the anomalous pathway (stippled area) to the atria. Because the atria are now no longer refractory (due to the prolonged conduction through the atrionodal junction), they can respond, and a retrograde depolarization wave is recorded. This atrial stimulus can return once again to the A-V node, but finds it refractory, and no further impulse is conducted. If, however, the refractory period of the normal pathway were abbreviated (refractory ratio: R1 = X ; R2 = X + 3) and/or the degree of block were still further prolonged, the returning atrial impulse would find the normal pathway nonrefractory and would then be conducted, thereby perpetuating a reciprocal cycle and effecting a reversed reciprocal rhythm. This is continued until an increase in the refractory period of the A-V node (due, for example, to vagal stimulation) terminates the cycle.

Relationship to the WPW Syndrome.—It is now generally accepted that the complexes of the WPW syndrome are due to conduction, in part, through an anomalous pathway. This is illustrated in Diagram A of Fig. 7. The refractory ratio is R1 = X ; R2 = X. This does not necessarily imply that the refractory periods are equal, but rather that the arrival of the atrial impulse at the atrionodal junction finds both pathways nonrefractory. Thus, for example, although the pathways may have unequal refractory periods (Fig. 8), the sinus frequency is such that arrival of the impulse at the A-V node (position 2 of Fig. 8) falls outside the refractory periods of both pathways. In effect, therefore, both refractory periods may be considered to be equal. It could be readily appreciated, however, that an increase in sinus impulse frequency (atrial impulse now in position 3 of Fig. 8) would make the unequal refractory periods apparent and effectual. Thus, with refractory periods in effect equal, the sinus impulse (at a slow atrial discharge frequency) is conducted through both pathways simultaneously, but with greater speed through the anomalous route, causing the typical fusion complex of the WPW syndrome. With an increase in rate, or marked increase in the discrepancy of the refractory periods, the refractory ratio

becomes R1 = X ; R2 = X + 3 (Diagram B of Fig. 7). The sinus impulse now finds the anomalous pathway refractory, is conducted through the normal pathway to the ventricles, returns in a retrograde direction through the anomalous pathway to the atria, finds the atria refractory (due to their prior stimulation by the sinus impulse), and is conducted once again through the normal pathway which has now recovered. This perpetuates the cycle and results in a paroxysmal tachycardia. Some of the characteristics of the *tachycardia* of the WPW syndrome now become apparent. First, the disappearance of the typical fusion complexes is due to anterograde conduction *entirely* through the normal pathway. Secondly, the frequent lack of P waves is due to the refractory state of the atria.

It seems, therefore, that in reversed reciprocal rhythm and in the WPW syndrome the basic defect is probably the presence of an anomalous pathway (congenital in origin). Reversed reciprocal rhythm, in addition, has a degree of anterograde and/or retrograde block. It is interesting to note that Wolff,[16] in a recent publication, has shown both patterns in the same graph.

CONCLUSION

It is postulated that both reversed reciprocal rhythm and the WPW syndrome are due to the presence of an anomalous A-V conduction pathway in addition to the normal pathway, and that the fundamental difference between these two conditions is the presence of a degree of A-V block in reversed reciprocal rhythm. The different patterns encountered in the two conditions are due to differing refractory ratios of the normal and anomalous pathways.

SUMMARY

1. A case of reversed reciprocating paroxysmal tachycardia is described.
2. This arrhythmia was very sensitive to vagal stimulation, which caused interesting patterns of group beating.
3. The mechanism of reversed reciprocal rhythm is explained on the basis of an anomalous pathway and a degree of anterograde block through the A-V node.
4. A hypothesis is advanced linking reversed reciprocal rhythm with the WPW syndrome.

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Effects of Atrial Fibrillation Upon the Circulation in Patients With Mitral Stenosis

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Atrial fibrillation is known to occur in approximately 40 per cent of the cases of mitral stenosis.[1,2] Uncontrolled atrial fibrillation often causes disabling cardiac symptoms, which may disappear when the ventricular rate is slowed by the administration of digitalis. However, even adequately controlled atrial fibrillation is considered a highly undesirable complication of mitral stenosis, primarily because it enhances the formation of mural thrombi, providing a threat of embolic phenomena. Furthermore, it is generally believed that controlled atrial fibrillation may affect adversely circulatory dynamics by exaggerating the circulatory embarrassment that may be caused by stenosis of the mitral orifice. It was noted[2-4] that patients with atrial fibrillation have, on the average, lower cardiac output, higher pulmonary vascular resistance, and higher left atrial and pulmonary arterial pressures than do patients with mitral stenosis in sinus rhythm. However, it has not been hitherto ascertained whether these differences reflect merely the well-known fact that atrial fibrillation is apt to appear in more advanced cases of mitral stenosis and in patients of more advanced age, or whether such differences are genuinely related to the effects of the arrhythmia per se.

The purpose of this investigation was to examine hemodynamic differences between patients with mitral stenosis in sinus rhythm and those in atrial fibrillation, attempting to eliminate all factors that affect the circulation except for the presence or the absence of atrial fibrillation.

MATERIAL AND METHODS

The series to be reported here consisted of 67 patients with mitral stenosis who underwent a careful clinical study, including a detailed history and physical examination, roentgenographic, fluoroscopic, electrocardiographic, and phonocardiographic examinations. On the basis of such a survey, all patients were considered to have significant mitral valvular disease, with either pure or predominant stenosis of the mitral orifice. Hemodynamic studies were performed at the time when the patient was considered to be in a stable state; that is, no retention of fluid was thought

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to be present, signs of cardiac failure were brought under control, and, in patients with atrial fibrillation, the ventricular rate was brought to an optimal level with the aid of a digitalis preparation. Patients represented a wide variety of severity of mitral stenosis, and varied from totally asymptomatic to those with advanced cardiac disability. Forty-eight patients were in sinus rhythm, and 19 patients were in atrial fibrillation. In 3 patients, two hemodynamic studies were performed, once when they were in sinus rhythm and once when they were in atrial fibrillation.

Hemodynamic measurements were performed during cardiac catheterization. This procedure was performed in the usual manner, using the technique reported in earlier communications.[5,6] Cardiac output was measured using the Fick principle, with at least two resting determinations and one during the last 3 minutes of a 6-minute exercise period. Pulmonary vascular resistances and the area of the mitral valve were calculated using the well-known formulae.[5]

RESULTS

Three important measurements taken during the hemodynamic study in all of the patients with mitral stenosis were analyzed, and a comparison between patients in artial fibrillation and those in normal sinus rhythm was made. These measurements were: the resting cardiac output, the pulmonary arterial wedge pressure (indirect left atrial pressure), and the pulmonary vascular resistance. Because of the most common occurrence of atrial fibrillation in patients with more severe forms of mitral stenosis, a comparison of patients with and without atrial fibrillation had to be made, with due consideration to the degree of mitral block. In order to fulfill this requirement, graphs were constructed in which each of the aforementioned measurements was plotted against the calculated area of the mitral valve, and each patient was shown as being either in sinus rhythm or in atrial fibrillation. Fig. 1 presents such relationship concerning the resting cardiac output. It is seen that patients with milder mitral stenosis show predominantly sinus rhythm, and those with more severe stenosis show mostly atrial fibrillation. With comparable severity of mitral stenosis, the average position of patients with atrial fibrillation is lower on the graph, implying an average

TABLE I. SUMMARY OF FINDINGS IN 3 PATIENTS STUDIED IN SINUS RHYTHM AND IN ATRIAL FIBRILLATION

PATIENT, SEX, AGE	RHYTHM	DATE	MVA (CM.²)	PAW PRESSURE (MM. Hg)	PA MEAN PRESSURE (MM. Hg)		CO (L./MIN./M.²)		HR
					(r)	(ex)	(r)	(ex)	(r)
1. H. C.	AF	Dec. 1957	0.9	23	36	60	2.5	3.4	80
M, 39	NSR	Jan. 1958	0.9	30	42	66	2.9	3.6	75
2. W. H.	NSR	Sept. 1954	0.9	22	32	51	2.6	3.9	70
M, 38	AF	Oct. 1957	0.9	18	27	54	2.2	2.2	62
3. B.W.	NSR	Apr. 1957	—	—	55	60	3.4	4.9	65
M, 36	AF	Jan. 1958	—	—	60	70	2.9	3.7	66

MVA = Mitral valvular area. PAW = Pulmonary arterial wedge. PA = Pulmonary artery. CO = Cardiac output. HR = Heart rate. r = Resting value. ex = Exercise value. NSR = Normal sinus rhythm. AF = Atrial fibrillation.

lower resting cardiac output. Fig. 2 presents, in a similar manner, the level of left atrial pressure, demonstrating that patients in atrial fibrillation showed, on the average, lower left atrial pressures than did those in sinus rhythm. Fig. 3 shows no apparent difference between the two groups in the incidence of elevated pulmonary vascular resistance.

Table I presents the essential hemodynamic findings in 3 patients with mitral stenosis who were studied while in atrial fibrillation and also while in sinus rhythm. All 3 of them showed lower resting cardiac output during atrial fibrillation. One of them showed, in addition, fixed cardiac output during exercise when in atrial fibrillation, but a satisfactory increase in the output with exercise when in sinus rhythm (W.H.).

TABLE II. HEMODYNAMIC FINDINGS IN 15 MATCHED PAIRS OF PATIENTS WITH MITRAL STENOSIS, ONE IN SINUS RHYTHM AND ONE IN ATRIAL FIBRILLATION (EACH MATCHED PAIR IS PRESENTED IN THE SAME LINE)

PATIENT	AGE	SINUS RHYTHM								
		MVA (CM.^{2})	HR (r)	HR (ex)	CO (r) (L./MIN./M.^{2})	CO (ex)	PW (r)	PA (r) (MM. Hg)	PA (ex)	PVR (DYNES SEC. CM.$^{-5}$)
M.	38	0.5	78	100	1.8	2.3	27	70	99	800
G.	27	0.6	70	90	2.1	2.8	27	33	49	133
L.	33	0.6	85	105	2.3	2.9	35	48	90	625
B.	44	0.7	60	120	2.4	2.2	40	72	105	500
B.	29	0.7	70	80	2.6	2.7	28	35	45	118
W.	45	0.8	80	96	2.8	2.9	30	37	60	112
W.	47	0.8	90	108	3.4	3.6	36	63	84	422
R.	37	0.7	80	96	2.3	2.9	30	56	88	580
H.	51	0.8	60	—	2.6	—	27	62	—	500
C.	34	1.0	75	100	2.4	2.9	20	25	48	80
D.	39	0.8	75	85	2.1	2.8	24	27	32	70
K.	37	1.1	65	75	2.7	3.0	18	23	30	82
C.	51	1.0	58	66	1.8	3.0	15	19	32	80
B.	55	1.1	70	140	2.4	3.3	20	28	38	140
T.	42	1.2	60	88	2.6	4.2	18	23	25	95
Mean	40.6	0.82	73	92.5	2.42	2.96	26.3	42.5	58.8	289

MVA = Mitral valvular area. HR = Heart rate. CO = Cardiac output. PW = Pulmonary arterial wedge pressure. PA = Pulmonary arterial pressure. PVR = Pulmonary vascular resistance. r = Resting value. ex = Value during exercise.

A comparison of circulatory dynamics during sinus rhythm and during atrial fibrillation in the same patient is the ideal way to approach the problem stated in the introduction. However, in this series the number of such cases was not only too small to answer the question adequately but also, in 2 of the 3 cases, the hemodynamic studies were widely separated, making it impossible to rule out the interplay of factors other than the cardiac rhythm. It was considered necessary, therefore, to use still another way of comparing the two groups. The material at hand was found to be adequate to evaluate statistically 15 pairs of

patients matched closely in regard to mitral valvular area and to age and, whenever possible, in regard to cardiac rate. This last parameter presented some difficulty, for in 3 patients the resting rate, and in 2 patients the rate during exercise, varied by more than 20 beats per minute. However, this was found acceptable, because in all patients included in the analysis the clinical evidence indicated that atrial fibrillation was adequately controlled by digitalis, and the rate appeared to have been optimal for the individual. Thus, the 15 pairs, presented in Table II, vary in one important respect only: one patient is in sinus rhythm and the other is in atrial fibrillation. It is seen that patients in atrial fibrillation had lower cardiac output in 12 instances, the average difference being 0.37 L./min./M.^{2}, with a standard error of 0.12; this average difference is significantly different from zero at the 1 per cent level by the use of the t-test.

TABLE II.—Continued

PATIENT	AGE	ATRIAL FIBRILLATION								
							MEAN PRESSURES			
		MVA (CM.^{2})	HR (r)	HR (ex)	CO (r)	CO (ex)	PW (r)	PA (r)	PA (ex)	PVR (DYNES SEC. CM.$^{-5}$)
					(L./MIN./M.^{2})		(MM. Hg)			
F.	34	0.5	75	110	1.7	1.8	27	63	90	990
A.	30	0.6	62	80	1.6	1.9	23	39	64	420
U.	36	0.6	85	110	1.5	2.1	30	36	60	165
J.	43	0.7	90	110	2.0	2.5	23	38	55	400
C.	28	0.7	65	95	1.9	2.2	24	40	45	385
S.	49	0.7	70	80	1.8	2.9	21	30	48	220
D.	49	0.7	70	100	2.5	—	32	72	87	750
K.	48	0.7	80	105	1.9	3.1	27	31	60	75
D.	53	0.9	70	85	2.9	3.2	27	45	72	260
L.	33	0.9	56	90	1.7	2.2	17	25	36	208
H.	38	0.9	60	78	2.6	2.4	22	32	54	190
K.	31	1.0	60	76	2.1	2.6	17	21	25	100
V.	46	1.0	88	156	1.7	1.7	20	27	52	200
S.	56	1.1	70	92	2.0	2.6	16	26	31	200
H.	52	1.3	80	96	2.9	2.9	14	22	48	130
Mean	40.5	0.82	72	97.5	2.05	2.43	22.8	36.4	55.1	312.8

Similarly, in 11 of the 13 matched pairs of patients in whom measurements were made during exercise the cardiac output during exercise was smaller in those with atrial fibrillation. The average difference here was 0.54 L./min./M.^{2}, with a standard error of 0.14. This is also significantly different from zero at the 1 per cent level by the use of the t-test. Pulmonary wedge pressure shows a difference between the two groups of 3.67 mm. Hg, with a standard error of 1.24. This difference is significant at the 5 per cent level.

On the other hand, pulmonary arterial pressures showed no significant difference, either at rest or during exercise. The resting pressure was less in patients with atrial fibrillation in 10 of 15 pairs, but the average difference of

6.13 was not significantly different from zero, since its standard error was 3.6. The pulmonary arterial pressure during exercise was less in patients with atrial fibrillation in 9 of 14 pairs, with an average difference of 4.50 mm. Hg, and the standard error of 5.72. Pulmonary vascular resistance was lower in atrial fibrillation 11 out of 15 times, the average difference being 23.7 dynes sec. cm.$^{-5}$, with a standard error of 58.4, the difference not being significant.

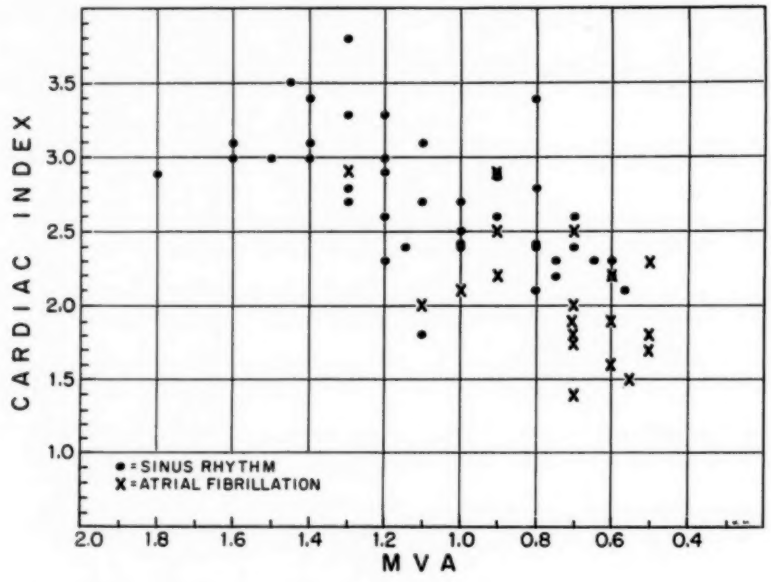

Fig. 1.—Relationship between cardiac output and mitral valvular area in patients with mitral stenosis who were in sinus rhythm and in atrial fibrillation. Ordinate: cardiac output expressed as index in liters/minute/M.^{2}. Abscissa: calculated mitral valvular area in cm.^{2}.

DISCUSSION

Two aspects of the problem of atrial fibrillation in patients with mitral stenosis have been under investigation in this study. The first aspect is the occurrence and severity of hemodynamic abnormalities in patients with atrial fibrillation as compared with those in sinus rhythm. By plotting the three principal hemodynamic measurements against the calculated area of the mitral valve in Figs. 1 to 3, it has been clearly demonstrated that the more frequent occurrence of severe hemodynamic abnormalities in association with atrial fibrillation is related to the more common occurrence of this arrhythmia in more severe cases of mitral stenosis.

The second aspect of the problem is the effect of atrial fibrillation per se upon the performance of the heart. This has been approached by the method of comparing findings in matching pairs of patients, whereby three other variables have been kept constant: the severity of mitral stenosis, the age of the patient, and the adequacy of control of cardiac rate. This last factor is probably the most crucial of the three. On theoretical grounds it is clear that atrial fibrillation can affect the circulation in two ways: (a) by reducing the late diastolic ventricular filling because of the absence of atrial contraction, and (b) by the varying length

of the diastole and the frequent presence of ineffective ventricular contractions, which affect adversely the efficiency of the heart. Both of these factors are minimized in the presence of slower ventricular rates and are exaggerated with rapid rates. That atrial fibrillation with uncontrolled ventricular rates may have serious circulatory consequences is well known from clinical observations, but it has been recently suggested that such an arrhythmia may even permanently damage the myocardium, presumably by persistently inadequate coronary flow.[7]

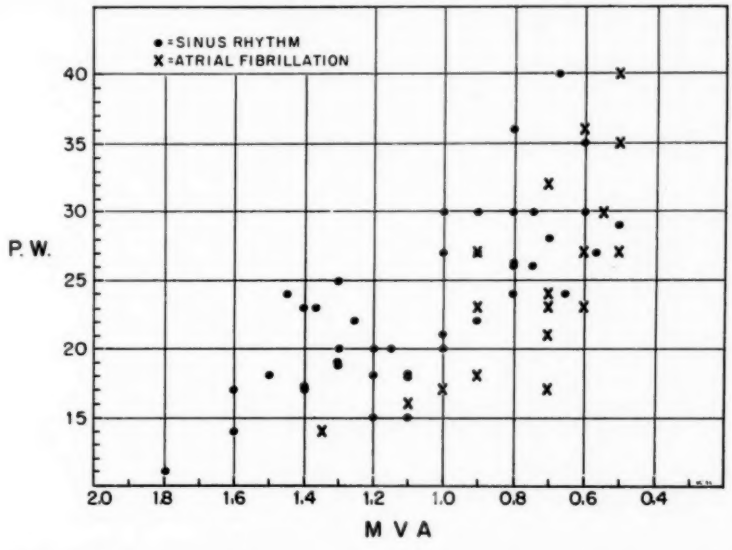

Fig. 2.—Relationship between pulmonary arterial wedge pressure and mitral valvular area in patients with mitral stenosis in sinus rhythm and in atrial fibrillation. Ordinate: mean pulmonary arterial wedge pressure in mm. Hg. Abscissa: calculated mitral valvular area in cm.^{2}.

In matching the pairs of patients with mitral stenosis in order to compare those with and those without atrial fibrillation, the severity of mitral valvular obstruction and the age of the patient presented no difficulty. Although the rate could not have been matched equally satisfactorily, the fact that the mean values for the two groups both at rest and during exercise varied less than 5 beats per minute suggests that the patients in atrial fibrillation were properly controlled by digitalis. Thus, the presence or absence of atrial fibrillation is thought to represent the only variable in the two groups. The analysis presented here shows that the measurements in which a statistically significant difference between patients with and those without atrial fibrillation was demonstrated are the cardiac output, both at rest and during exercise, and pulmonary wedge pressure. The output is shown to be about 20 per cent higher in patients with sinus mechanism than in those with atrial fibrillation. Pulmonary arterial pressures and pulmonary vascular resistance showed only minor and insignificant differences, mostly accountable for by the effect of lowered cardiac output in those with atrial fibrillation. It is evident that the lower level of left atrial pressure (pulmonary wedge pressure) is a direct consequence of lowered cardiac output. Since in mitral stenosis the left ventricular diastolic pressure is normal (between 5 and 10 mm. Hg), the elevated left atrial pressure level represents roughly the

pressure gradient across the mitral valve, which is the product of valvular resistance and flow through the valve. It follows that through similarly obstructed valves, left atrial pressure levels will be in direct relationship to cardiac output. Thus, lowered left atrial pressures in patients with atrial fibrillation are the direct consequence of lower cardiac output and do not constitute an independent hemodynamic alteration.

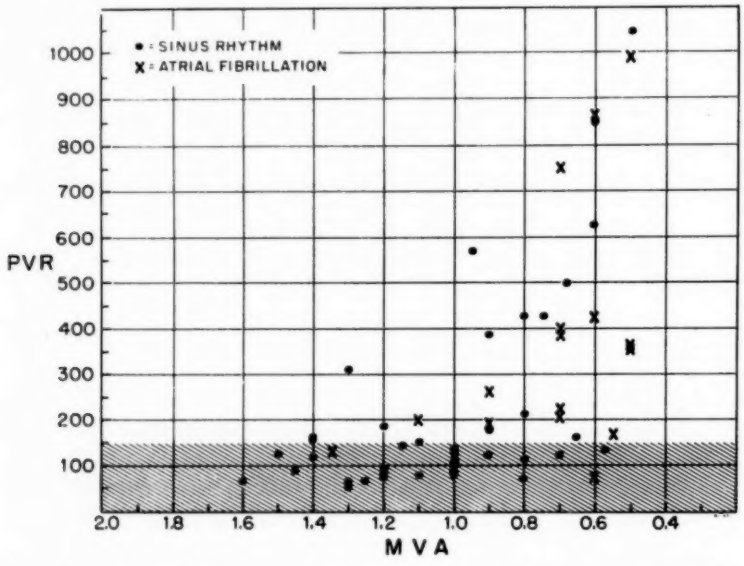

Fig. 3.—Relationship between pulmonary vascular resistance and mitral valvular area in patients with mitral stenosis in sinus rhythm and in atrial fibrillation. Ordinate: calculated pulmonary vascular resistance in dynes seconds cm.$^{-5}$. Abscissa: calculated mitral valvular area in cm.^{2}. Shaded area represents normal zone of pulmonary vascular resistance.

Previous studies dealing with hemodynamic effects of atrial fibrillation were performed on patients with normal hearts and with various cardiac conditions, including mitral stenosis. Results were largely inconclusive. Hecht and associates[8] studied 15 patients in fibrillation and after sinus rhythm had been restored, and found consistent improvement during sinus mechanism only with exercise. Kory and Meneely[9] found a significant increase in cardiac output at rest and in exercise in 6 of 8 patients studied in a similar manner. Hansen and his associates[10] showed an increase in resting cardiac output of more than 10 per cent in 8 out of 14 patients who were studied in fibrillation and then again at 3 weeks to 2 months after the sinus rhythm had been restored. Broch and Muller[11] studied 20 patients in atrial fibrillation, 11 of whom had mitral stenosis, and then repeated the study after restoration of sinus rhythm. They found a small, but statistically significant difference, in that the cardiac output during sinus rhythm was higher than during atrial fibrillation.

This brief analysis indicates that previous investigations showed, at best, a trend in the direction of a higher cardiac output during sinus rhythm than during atrial fibrillation. Yet in most of these studies, details are not available to determine two points: (a) whether other factors potentially affecting circulatory dynamics had been eliminated, making atrial fibrillation and sinus rhythm

the only variables in the two respective studies; and (b) whether a different circulatory response to atrial fibrillation could occur in mitral stenosis, in other forms of cardiac disease, and in normal hearts with idiopathic atrial fibrillation.

Findings of this study show that in patients with mitral stenosis the resting cardiac output is likely to be 20 per cent higher in sinus rhythm than in atrial fibrillation, under comparable circumstances, and that a difference of similar magnitude is likely to be found during exercise. To what extent this difference can affect the patient's symptomatology cannot be ascertained from data at hand: clinical symptomatology, with its large subjective angle, obviously cannot be compared in two patients in a manner similar to hemodynamic measurements. Studies in this laboratory demonstrated the variability of clinical symptomatology in patients with mitral stenosis,[12] and only crude parallelism between the degree of disability and the severity of mitral stenosis. This implies that lowering of the cardiac output is likely to affect different individuals differently. Yet, a 20 per cent increase in cardiac output coincidental with the restoration of sinus rhythm in a patient with mitral stenosis may be of considerable importance in alleviating cardiac symptoms, for a change of this magnitude is considered to be a satisfactory response to digitalization.[13]

This study was devoted to the problem of atrial fibrillation as a complication of mitral stenosis and, by virtue of its occurrence, dealt with atrial fibrillation in patients with significantly advanced mitral valvular obstruction. It is probable that atrial fibrillation occurring in other forms of advanced cardiac disease affects the circulation in a similar manner, inasmuch as hemodynamic abnormalities in mitral stenosis and in left ventricular failure show considerable similarities.[14]

SUMMARY AND CONCLUSIONS

The effect of atrial fibrillation upon circulatory dynamics was studied in a series of 67 patients with mitral stenosis, and an attempt made to evaluate its effect as the only variable factor.

The occurrence of more advanced circulatory abnormalities in patients with atrial fibrillation as compared to those with sinus rhythm was confirmed, but was shown to be related primarily to the more common occurrence of atrial fibrillation in advanced cases of mitral stenosis.

Three patients with mitral stenosis were studied twice, once in sinus rhythm and once in atrial fibrillation. In addition, 15 pairs of patients, matched in all respects except for cardiac rhythm, were compared in regard to hemodynamic findings. The level of pulmonary arterial pressures and the pulmonary vascular resistance showed no significant difference between patients in sinus rhythm and those in atrial fibrillation, and between the two studies performed in the same patients. The cardiac output, however, was found to be consistently higher in patients in sinus rhythm than in those in atrial fibrillation, the mean difference being approximately 20 per cent both at rest and during exercise. This difference was found to be statistically significant at the 1 per cent level. The level of left atrial pressure, significantly lower in fibrillators, was considered a secondary response to lower cardiac output.

Thus it is concluded that atrial fibrillation, even under optimal digitalis control, tends to lower significantly the cardiac output in patients with mitral stenosis. Even though this difference is relatively small, it is believed that in some such patients the development of atrial fibrillation could accentuate, and restoration of sinus rhythm minimize, clinical disability.

The author is indebted to Dr. Lincoln E. Moses, Associate Professor of Statistics, Stanford University, for the statistical evaluation of the data.

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Action of Hypoglycemia on Coronary Insufficiency and Mechanism of ECG Alterations

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With the increase of coronary sclerosis paralleling the increasing level of civilization, on the one hand,[1] and a better understanding of the relationship between diabetes and arteriosclerosis, on the other hand, it has recently been found that diseases of the heart and circulation play the main role in diabetic mortality.[2-11] At the same time it has been reported that in the course of hypoglycemic attacks occurring in diabetic patients as a result of an increased use of insulin,[12] episodes of angina pectoris and acute coronary thrombosis are being frequently encountered,[13-15] and that, in such patients, ECG recordings evidencing changes induced by coronary insufficiency have been observed.[16] As a consequence, certain authors have postulated that hypoglycemia was to be held responsible for angina pectoris and myocardial infarction,[3,17] whereas others insist that such cases are most unusual.[2,18-20]

The explanations offered concerning the relationship between hypoglycemia and coronary insufficiency are rather hypothetical in character, and different interpretations are to be found in the literature.[20-29] We have therefore undertaken some studies in order to gain insight into the more obscure aspects of this important problem.

METHOD AND MATERIAL

Sixteen patients with angina pectoris and 22 patients with acute and subacute myocardial infarction from our clinic were studied. The ages of our patients varied between 35 and 73 years, with a mean age of 53.9 years. In order to be able to use standard tests, we tried to confine our studies to patients who presented no alterations in carbohydrate (CH) metabolism, no endocrine diseases, as well as no heart failure, vomiting, diarrhea, renal insufficiency, etc., which could influence the electrolyte balance; patients who had taken digitalis were also excluded from this study. We divided our series of patients into four groups: *Group I:* 14 patients who had fasted for 14 hours were submitted to the insulin tolerance test[30,31]; ECG, glycemia, serum K, Na, and Ca were determined before and after insulin was given. *Group II:* 10 patients were given KCl intravenously and per os and were submitted to the single or double insulin test; ECG and electrolytic changes were recorded. *Group III:* 8 patients were given Regitine, 30 to 45 minutes after injection of insulin, and the same alterations were investigated. *Group IV:* 6 patients were given the epinephrine test,[32-34] and the same alterations were determined.

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ECG recordings were made by means of the Sanborn-Viso-Cardiette. Blood sugar was examined by the Hagedorn-Jensen method,[35] serum K by the Kramer-Tisdall method,[36] serum Na by the Rourke method,[37] and serum Ca by the Kramer-Howland method.[38]

RESULTS

Group I.—The 14 patients of Group I were given 0.2 units of insulin per kilogram of body weight. In this group, as in the others, no anginal pain was noted even at the maximal level of hypoglycemia.

ECG alterations: In no case could a change in P wave and P-R segment be seen. In 3 patients the amplitude of the R wave was definitely increased, and in 2 patients the S was deepened; no broadening of QRS was noted. In 11 patients there was an unwedging of RS-T of 1 to 6 mm. size. In 11 patients there was also a decrease in amplitude of the T wave or an inversion of the T wave. In 8 patients there was a formation of PAP waves, and in 1 patient a U wave was encountered. In 6 patients the Q-T was lengthened, in 1 patient it was decreased, and in the others it was unchanged. With the exception of one case, tachycardia occurred in all patients, especially at the forty-fifth minute after insulin, then gradually subsided. In 4 patients, extrasystoles occurred, and 1 patient showed paroxysmal tachycardia at the forty-fifth minute.

Glycemia: In all cases, marked hypoglycemia was found 30 to 45 minutes after the insulin was injected. By 120 minutes after the injection, glycemia was found to have reverted to normal.

Potassium: Potassium, which was found in amounts of 18.9 to 22.0 mg. per cent before the test, decreased parallelly with the hypoglycemia, and at 45 minutes after injection the lowest figures were recorded (10.6 to 17.0 mg. per cent). It is remarkable that at the lowest point of hypopotassemia, the ECG changes were most evident, and that hypopotassemia appeared later than hypoglycemia.

Sodium: Sodium, which was 316 to 416 mg. per cent before the test, followed a course opposite to that of potassium and increased to from 345 to 431 mg. per cent at 45 to 60 minutes after injection. Evidence of hypernatremia was seen to occur somewhat later than hypopotassemia.

Calcium: Calcium was found in amounts of 9.2 to 10.5 mg. per cent before the test, and showed no marked oscillations during the experiment.

Figs. 1, 2, 3, and 4 present the ECG, glycemia, and serum electrolyte findings in 2 patients of Group I.

Group II.—In 6 patients, 5 Gm. of KCl had been given per os before insulin (0.2 units per kilogram of body weight) was injected. In 3 patients, perfusion with 2 Gm. of KCl was made during the test. In 1 patient the perfusion with KCl was started when the ECG changes and hypopotassemia had already begun, and in 3 patients a second injection of insulin was made at 30, 45, and 60 minutes after start of the test.

Patients who had received insulin after potassium, as well as those who had received a second injection of insulin during the time of the test, demonstrated no ECG changes whatsoever. In one case in which ECG changes began as soon as the test was started, intravenous perfusion with potassium induced an im-

mediate normalization of these changes. It is noteworthy that 2 patients of Group I who had presented ECG changes after insulin had none of these ECG alterations when insulin was given together with KCl.

In those patients of Group II who had received KCl, hypopotassemia was not very marked, serum K increased but slightly, and serum Na decreased very slightly; as to serum Ca, a decrease was noted which did not occur in the other groups. Figs. 5 and 6 present the ECG and electrolyte findings in one of these patients.

Group III.—In the patients of this group, to whom Regitine (10 mg. intravenously) was given 30 minutes after the insulin, ECG changes were as conspicuous as in the first group. Glycemia was still abnormal 30 minutes after Regitine had been injected, and hypoglycemic figures were noted even at the end of the experiment. Parallelly, hypopotassemia and hypernatremia were prolonged, and no striking changes in calcemia were recorded. Graphic representation of the ECG and electrolytes of one patient of Group III are shown in Figs. 7 and 8.

Group IV.—In the 6 patients receiving subcutaneous injections of epinephrine, RS-T unwedging, extrasystoles, inversion of T, lengthening of Q-T, and formation of PAP waves were observed at from 5 to 120 minutes after the injection, as after the injection of insulin. ECG changes were nearly similar in the two experiments.

After injections of epinephrine, glycemia increased by 30 to 45 mg. per cent; parallelly, hypopotassemia and hypernatremia occurred. Serum Ca showed no marked change. The ECG and electrolyte findings in one patient of Group IV are graphically reported in Figs. 9 and 10.

DISCUSSION

A. *Glycemia and Electrolyte Changes.*—In those patients in whom insulin produced hypoglycemia together with hypopotassemia, this parallelism could be explained by the fact that through the action of insulin, glucose utilization was increased and potassium was drawn into the cell. Again through the action of insulin, the production of glucose-6-phosphatase is enhanced, which facilitates the penetration of glucose into the cell.[39] On the other hand, as during the hexokinase reaction, an acid equivalent is freed for each phospherized glucose molecule, the cell's interior pH moves over to the acid side, and in place of the H ions, which leave the cell, extracellular potassium enters the cell.[40]

In all of our patients, hypopotassemia followed hypernatremia, but with a few minutes' interval. The changes of Na ions in the metabolism of CH have not been exhaustively studied. Because a relation is known to exist between K and Na, it is surmised that some alterations will also occur with the latter ion. Under experimental and clinical conditions the intracellular behavior of Na and K run in opposite directions.[41] In previous experiments,[42] we, too, have been able to confirm the presence of the opposite movements of these ions. In order to explain them, it is necessary to remember the qualitative characters of these ions.[43] There are, within the cell, factors which regulate the indiffusible and diffusible fractions.

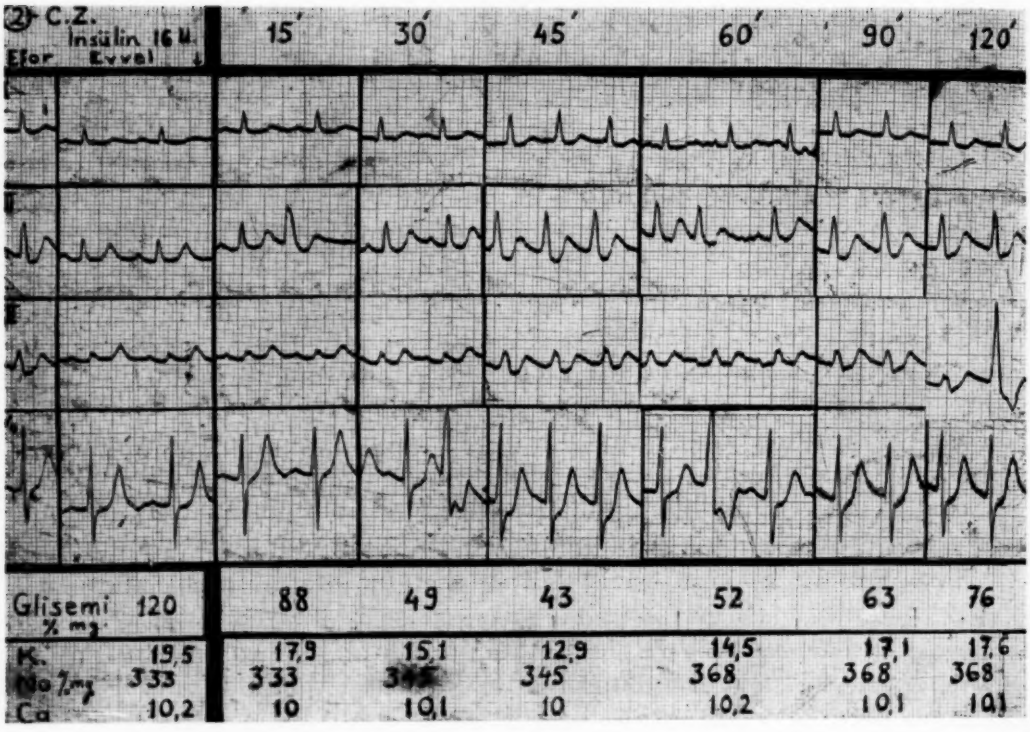

Fig. 1.—ECG alterations in a patient with angina pectoris under the influence of insulin: after 45 min., RS-T is lowered by 3 mm. in Lead II, by 4 mm. in Lead V_4, and K reaches its lowest serum level. After 120 min., potassemia has not yet reverted to normal, and RS-T changes have not entirely disappeared.

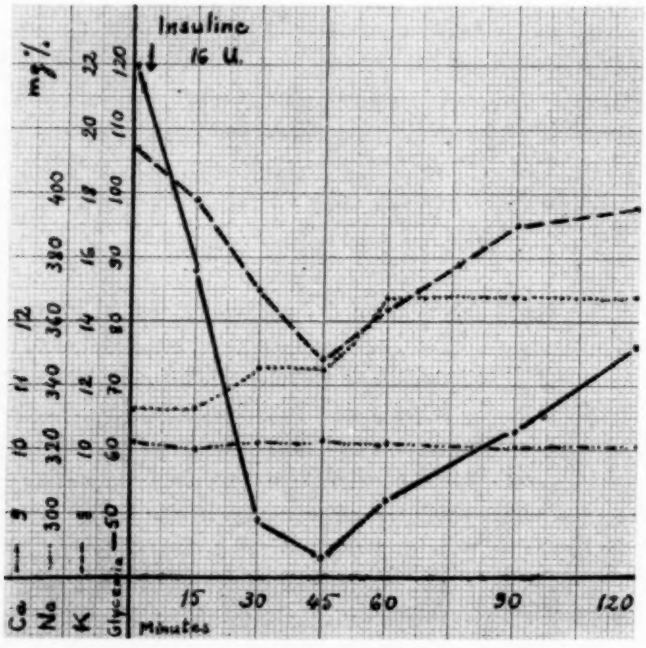

Fig. 2.—Graphics of blood sugar, K, Na, and Ca of same patient as in Fig. 1.

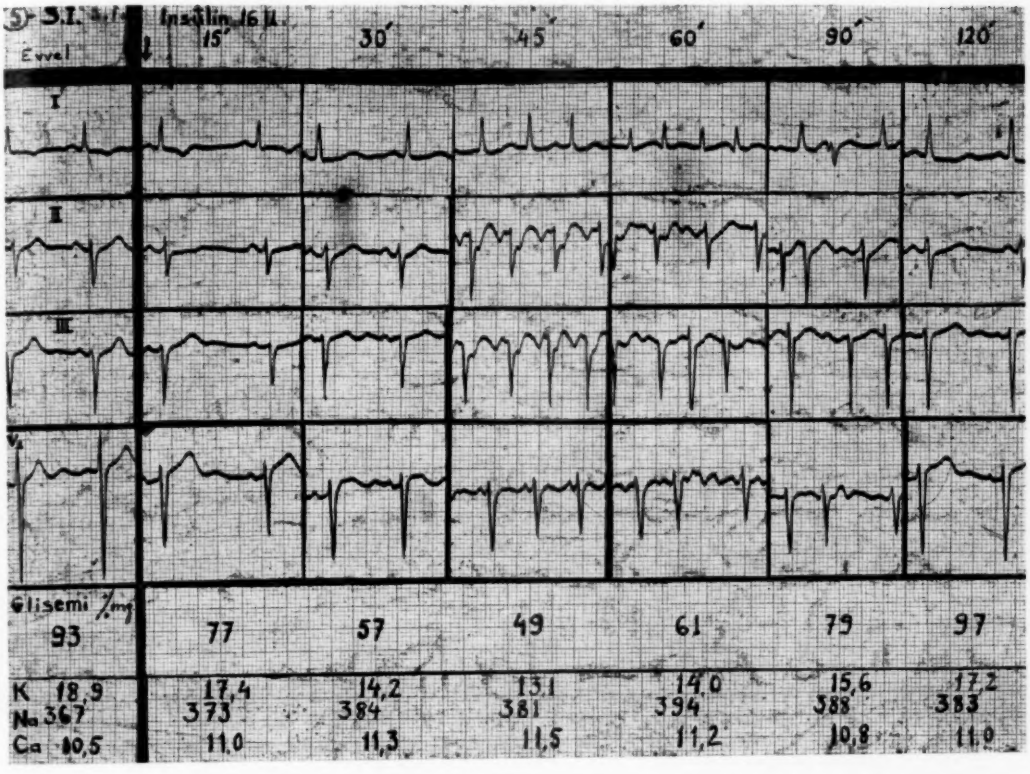

Fig. 3.—ECG alterations in a patient with old anterior myocardial infarct under the influence of insulin: after 30 min. there is inversion of T in Lead I; after 45 min., paroxysmal tachycardia. After 120 min., serum K has reverted to its initial level, and the ECG tracings to their previous aspect.

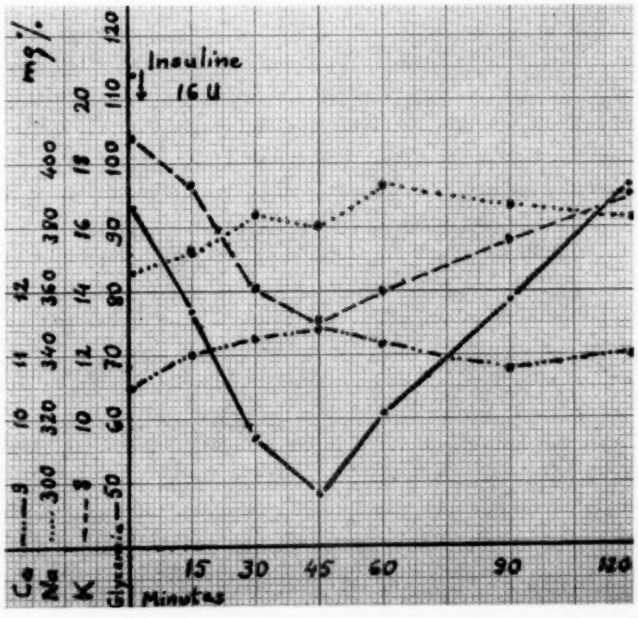

Fig. 4.—Blood sugar and electrolytes of same patient as in Fig. 3. After insulin, blood sugar and K decrease, Na increases. Ca changes are not marked.

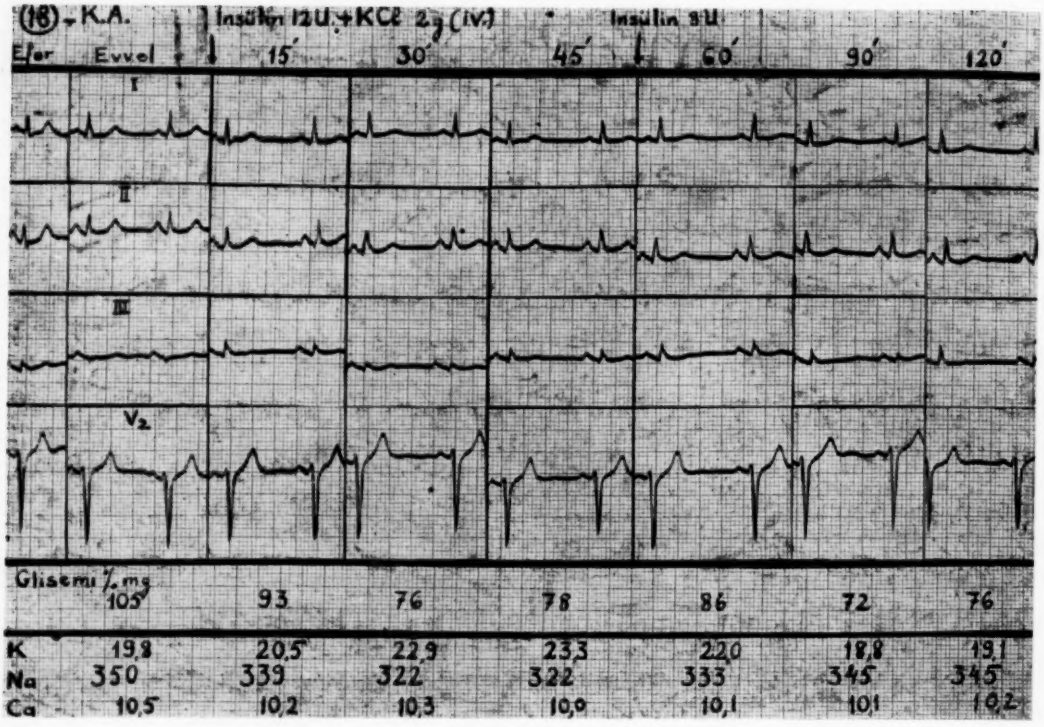

Fig. 5.—ECG of a patient with angina pectoris who was given a perfusion of 2 Gm. of KCl over a period of 2 hours; 12 units of insulin were given intravenously at the beginning of the experiment, and 8 units more were given 45 minutes later. Not the slightest ECG changes could be recorded.

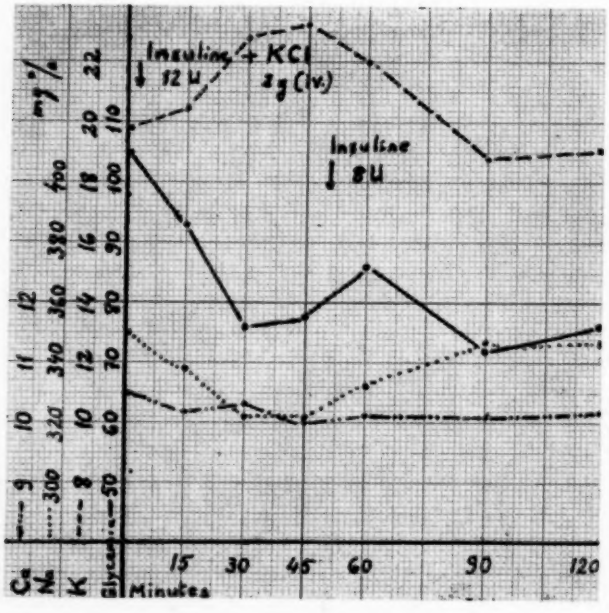

Fig. 6.—Same patient as in Fig. 5, who was given insulin while perfused with KCl. There was a slight fall in blood sugar, a slight increase in serum K, and a decrease in Na.

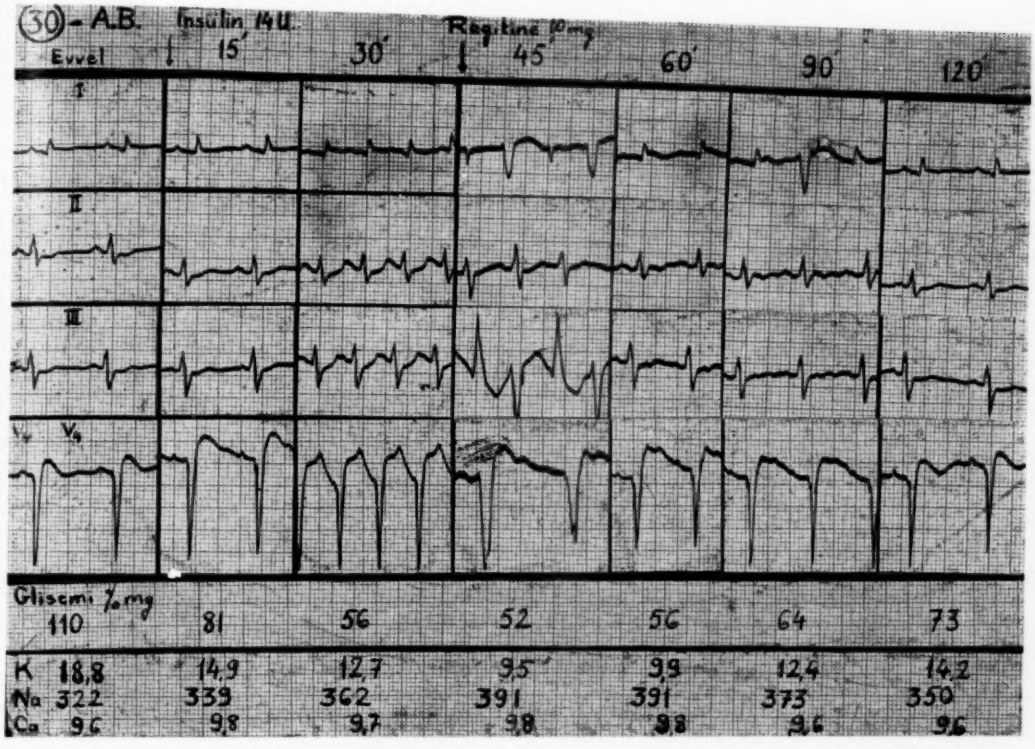

Fig. 7.—In a patient with a 3-month-old anteroseptal infarct, paroxysmal tachycardia started 30 min. after injection of insulin, and was not corrected by 10 mg. of Regitine injected at this time. Moreover, frequent extrasystoles and PAP and U waves were seen to occur, as well as further elevation of the RS-T segment, especially in Lead V_4.

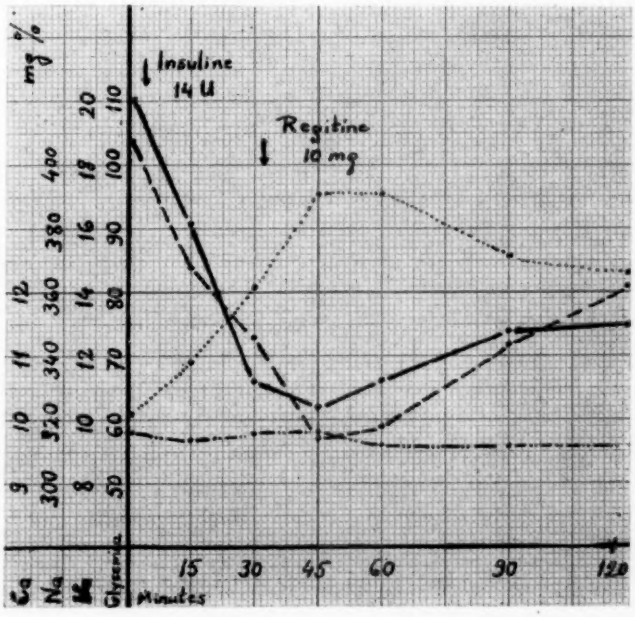

Fig. 8.—Hypoglycemia, hypopotassemia, and hypernatremia lasted longer in this patient who was given insulin and Regitine. Serum Ca remained unaltered.

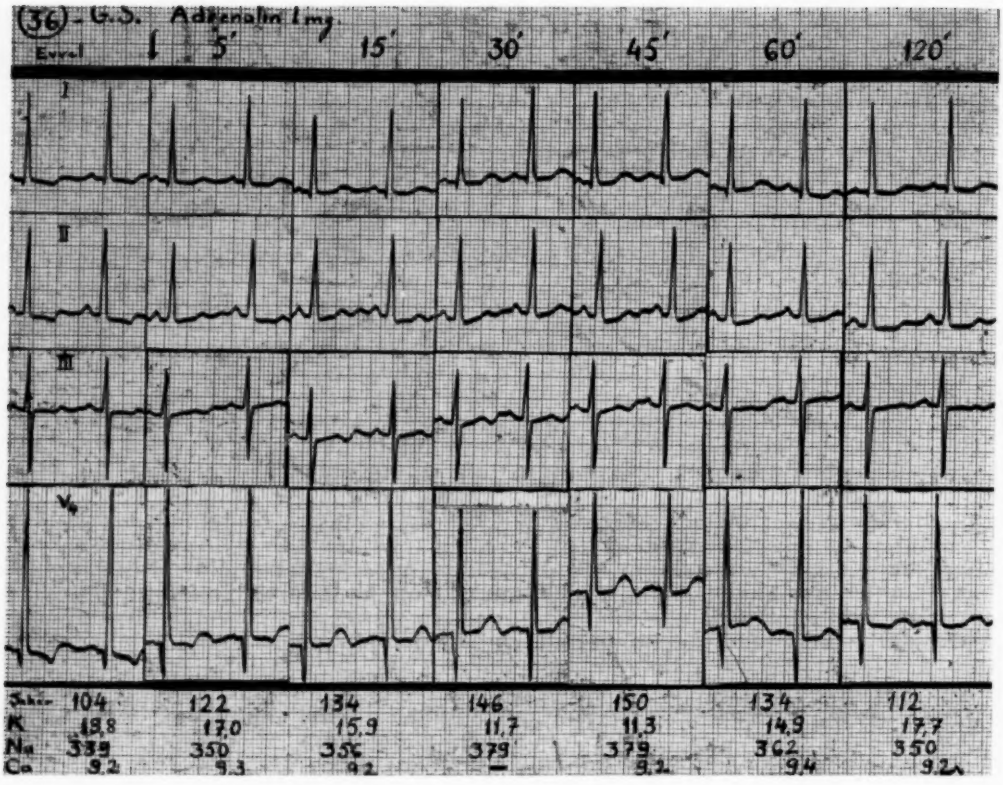

Fig. 9.—In a patient with old myocardial infarct the ECG changes produced by the subcutaneous injection of 1 mg. of epinephrine are the same as those resulting after insulin. After 5 min., T inversion and R-ST lowering is seen in all derivations. ECG tracings start to revert to their previous appearance only after 120 min.

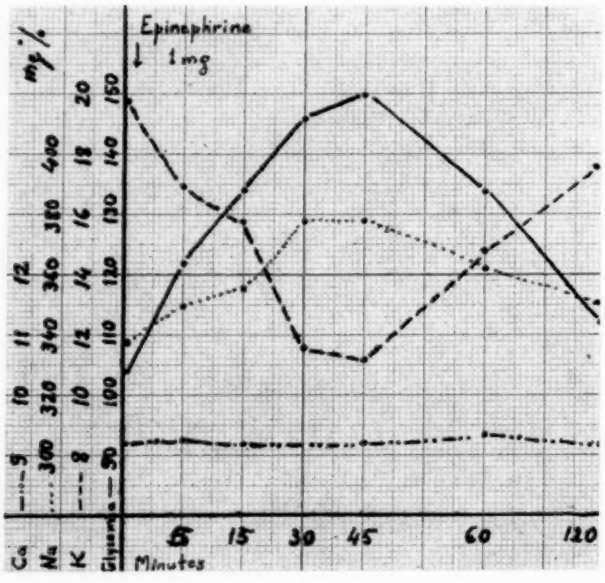

Fig. 10.—After injection of epinephrine, blood sugar increases, K decreases, and Na is slightly elevated. Serum Ca remains unchanged.

For instance, the balance between the intracellular indiffusible K and the active diffusible K can act on the proportion of diffusible intra- and extracellular K. The stability of this quotient is assured by the amount of K which leaves or enters the cell. During the synthesis of glycogen through the action of insulin, cellular K passes from one side of the membrane to the other; while intracellular K increases, extracellular K falls below normal. These movements cause the K gradient to be disturbed, which in turn upsets the balance between intra- and extracellular Na ions, and, thus, part of the intracellular Na leaves the cell.[44] The precedence of hypopotassemia over hypernatremia in our patients is a result of these movements; and, in our opinion, hypopotassemia plays a primary role, hypernatremia a secondary one, in the electrolyte exchange. However, during the phase of restitution, hypopotassemia as well as hypernatremia revert slowly to normal.

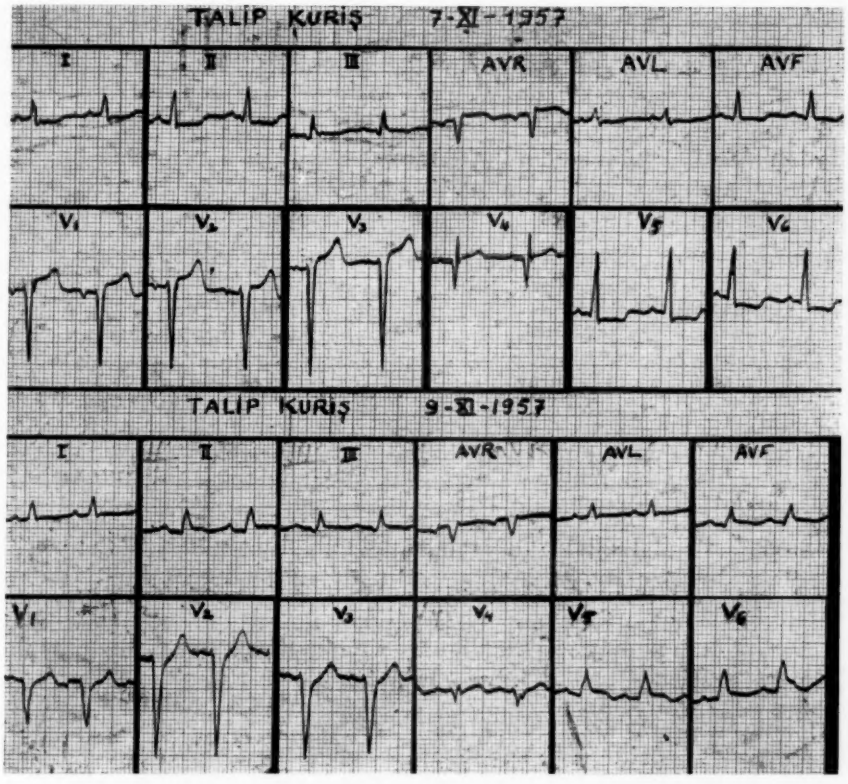

Fig. 11.—In a patient with diabetes and coronary sclerosis, a myocardial infarct eventually occurred during insulin therapy. At that time, glycemia was 385 per cent, and there was consequently no correlation between the infarct and insulin or hypoglycemia.

In the patients of this group, Ca showed no striking changes, the figures for it being mostly the same during the duration of the test; a lack of movement of Ca is also confirmed by the experiments of Clegg.[45] The reason that Ca does not participate in the movements of K and Na is that it does not particularly participate in the CH metabolism or the muscle metabolism.

As to the patients receiving injections of insulin after KCl had been given per os or intravenously, the fall in blood sugar was less pronounced, and glycemia promptly reverted to normal. Potassium, when it is given to the body from outside, acts in opposite direction in the metabolism of CH and produces hyperglycemia, which enhances glycogenolysis.[46-48] In those of our patients in whom K had been given together with insulin, hyperglycemia did not occur, but the fall in blood sugar was less than in the patients of Group I. In our opinion, this exogenous K enters rapidly into the cell and inhibits glycogenesis or stimulates glycogenolysis. As a matter of fact, when insulin was injected for the second time in the course of the experiment, the fact that the second dose of insulin was not able to increase the hypoglycemia is evidence for the inhibitory role of K. In this group of patients, serum K showed a gradual increase; in one patient this increase reached hyperpotassemic values, whereas in other patients it did not reach the limit of normal. In the patients to whom K was given, serum Na fell but little, and serum Ca was decreased by 1 mg. per cent.

In the patients to whom both insulin and Regitine were given, there was a delay in restitution, and the blood sugar maintained hypoglycemic values until the end of the experiment.* The reason is that epinephrine, which should have acted as a stimulus to glycogenesis in the restitution phase, was blocked. Parallelly, hypopotassemia and hypernatremia lasted longer, and calcemia also remained unaltered.

As to the patients who received epinephrine, their glycemia was increased, as compared to that of the others. On the other hand, they presented definite hypopotassemia and hypernatremia. Glycemia increased in this group mainly through the formation of glucose from liver glycogen and partly from glyconeogenesis as a result of the stimulation through the secretion of ACTH.[50,51]

In the patients injected with epinephrine, hyperglycemia was accompanied by hypopotassemia and slight hypernatremia; this hypopotassemia is the consequence of the fact that liver glucose and potassium are affected in the same fashion during their transport into the muscle cell. While K enters the cell, Na leaves it, and a slight hypernatremia occurs. There is no marked change in the Ca values in these patients.

B. *Electrocardiographic Alterations.*—Some of the ECG alterations which are to be seen in patients with insulin-induced hypoglycemia suggest mainly an anoxemia of the myocardium. However, there was no single instance of anginal pain during these alterations, which subsided completely and spontaneously within 30 to 60 minutes. The fact that there was no anginal pain even in the patients in whom the RS-T unwedging amounted to 3 to 6 mm. makes it unlikely that the alterations were caused by anoxemia. On the other hand, accompaniment of the signs of hypoglycemia by marked asthenia and adynamia, and the fact that the ECG alterations occurred at the time at which serum K varied between 9 and 15 mg. per cent suggest that hypopotassemia played a major role here.

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*Regitine (Ciba) which is a member of the imidazoline group acts as an antagonist to epinephrine and norepinephrine. At the same time it has an adrenolytic and sympatholytic action.

ECG changes after epinephrine are identical with the changes after insulin and parallel to the variations in electrolytes. Instead of giving potassium prophylactically or therapeutically in order to correct these changes, and inasmuch as the experiment with potassium had been previously done along with insulin, we preferred to use Regitine, for the purpose of neutralizing directly the effect of epinephrine. In this way, the action of epinephrine was blocked and, as a consequence, the rate decreased, whereas S-T and T changes were seen to persist.

The decrease in the concentration of K disturbs the K gradient toward the cell, and K enhances the excitability: thus, the transmembrane action potential is altered and the well-known hypopotassemic ECG alterations appear. As to the previously mentioned ECG alterations presented by the patients with coronary sclerosis who received injections of insulin, these alterations are identical with hypopotassemic ECG alterations.[22,53] They are most prominent at the moment at which serum K is lowest, which fact shows their relation to hypopotassemia; on the other hand, in the patients of Group II, whether KCl was given together with insulin, or whether a second dose of insulin was administered 30 to 45 minutes after the first, there were no ECG changes. Moreover, changes in the ECG were immediately normalized by perfusion with potassium; all these facts demonstrate the important role played by potassium in the production of ECG changes. Contradicting this assumption of ours are the instances reported in the literature of anginal pain increasing after injection of insulin, and even instances of myocardial infarction. But a close survey of these reports shows that the cases dealt with were not well-followed ones.[15,54] In this context we have had a patient on whom a brief report follows:

The patient was a 57-year-old man who had been diabetic since 9 years of age, and who used insulin irregularly. On admission to our clinic, his blood sugar was 385 mg. per cent or more. His blood pressure was 140/90 mm. Hg, and his ECG presented evidence of left cardiac strain. He was put on a regimen of 150 CH with 15-20-15, i.e., a total of 50 units of insulin a day. One morning two days later the patient was found with perspiration, tachycardia, and hypotension (95/70 mm. Hg). Examinations made at that moment revealed a blood sugar of 385 mg. per cent, and a white blood cell count of 10,400. The ECG presented signs of marked necrosis and ischemia in Leads V_4, V_5, and V_6 (Fig. 11). If glycemia had not been determined in this case at the time of the infarct, the perspiration, tachycardia, etc., which were present would have been attributed to hypoglycemia, and insulin would have been held responsible for the infarct.

The presence of a similar ECG in the patients of Group IV who had received epinephrine could have suggested that the electrocardiographic alterations were the consequence of an epinephrine secretion following the hypoglycemia; however, the presence of hyperglycemia with hypopotassemia and hypernatremia after the injection of epinephrine shows that they were related to the disturbance of the electrolyte balance. Still more important is the fact that in the patients who received Regitine, as a blocking agent to epinephrine (Group III), the ECG alterations, far from disappearing, were even more marked and persistent. Regitine caused hypoglycemia and hypopotassemia to persist and enhanced the ECG changes.

C. *Mechanism of ECG Alterations.*—According to Lenzi,[43] the contractions of myocardial muscle fibers depend on the changes in intra- and extracellular

concentrations of K and Na. Fleckenstein[55] affirms that during the contraction and relaxation phases of the muscle, Na and K are changing constantly. But these variations are limited in extent, and the changes beneath one side of the cell membrane are always balanced by changes taking place on the other side. This balance is called "gradient." Fleckenstein and Hertel[56] have shown that the increase in intracellular K and decrease in Na provoke the muscular contraction. The energy of this contraction is not chemical or enzymatic in character, but is produced by the diffusion between K and Na, whereas it has been shown that the ion Ca has but little effect on the muscular contraction. In the end, the cation concentration differences are also transformed into electrical potential.

Our experiences prove very clearly that during hypoglycemia, K first enters the cell and disturbs the K gradient. In fact, the decrease of serum K occurs 15 to 30 minutes after the injection of insulin. When K has entered the cell, the mechanical and electrical potentials increase, thus causing contraction and depolarization. This situation causes the axis rotation, which we observed in our cases.

When the K gradient is disturbed, the K/Na balance is also upset, and intracellular Na leaves the cell. Thus, the Na gradient is also disturbed. This condition increases the perifibrillary tension and causes the repolarization potential to augment, which in turn causes changes in the T wave and the formation of PAP and U waves.

At the moment when hypopotassemia is maximal, a maximal amount of K ions gathers within the cell; the excitability is extreme and facilitates the appearance of the extrasystoles and paroxysmal tachycardia which we observed in some patients.

The RS-T changes which we recorded in some of our patients were most probably also related to the disturbed K gradient, because the entrance of K into the cell increases the relaxation potential of the cell and causes RS-T to descend below the isoelectric line.

As to lengthening of Q-T, which does not appear in every case, it is possible that it could be related to a disturbance of the K/Ca relation. But it is more likely that the Q-T segment appears to be lengthened, whereas in fact the T-U waves are superposed.

SUMMARY

Thirty-eight patients with coronary sclerosis (16 with angina pectoris and 22 with myocardial infarction) were examined after injections of insulin, epinephrine, insulin-Regitine, and insulin-KCl, as to their ECG, glycemia, serum K, Na, and Ca.

The ECG alterations which appeared, whether through the action of insulin or of epinephrine, seem to be related to hypopotassemia or a slight hypernatremia; a sympathicolytic drug (Regitine) which inhibits epinephrine prolongs the duration of hypopotassemia and hypernatremia, so that with this drug the ECG

alterations are more marked. KCl given intravenously or per os prevents the formation of these ECG alterations. During these experiments no clear-cut oscillations of the Ca ion were noted.

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An Electrocardiographic Estimation of the Pulmonary Vascular Obstruction in 80 Patients With Mitral Stenosis

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Obstruction to pulmonary blood flow is a major hemodynamic abnormality in patients with mitral stenosis and plays an important role in determining their clinical course.[1]

Wood[2] has stated that the level of pulmonary vascular resistance in mitral stenosis closely parallels the degree of right ventricular preponderance indicated in the electrocardiogram. Contrariwise, Trounce[3] had concluded that in mitral stenosis the correlation was variable between the electrocardiographic signs of right ventricular hypertrophy and the pulmonary arterial pressure. Furthermore, as recently emphasized by Milnor,[4] the electrocardiographic criteria for the diagnosis of right ventricular hypertrophy are not entirely satisfactory, for electrocardiographic signs of right ventricular predominance may occur in the absence of pathologic evidence of right ventricular hypertrophy. Hence, the present study was undertaken to ascertain whether a quantitative correlation could be found between the electrocardiograms of patients with mitral stenosis and the degree of increase in their pulmonary vascular resistance. As one of us and Robinson have reported previously on the electrocardiographic findings in mitral valvular disease,[5] the previously described electrocardiographic categories were compared also with the pressure flow relationships in the pulmonary vascular bed.

MATERIAL AND METHODS

The clinical, electrocardiographic, and hemodynamic data from 80 adult patients were analyzed. In all cases, mitral stenosis had been established as the predominant valvular lesion from the characteristic clinical and laboratory (cardiac catheterization) findings. This diagnosis was confirmed at the time of mitral valvotomy in 76 of the 80 patients; in the remaining 4, mitral stenosis was the major valvular lesion found at necropsy. The mitral valvotomies were performed by either Dr. J. W. Kirklin or Dr. F. Henry Ellis, Jr., to whom we are indebted for detailed reports on the degree of mitral stenosis and insufficiency present at the time of commissurotomy. Patients who had associated systemic arterial hypertension or significant aortic or tricuspid valvular disease were not included in this study.

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Of the 80 patients, 53 were women and 27 were men, a ratio of 2 to 1. The average ages were 37 years (range, 18 to 58) for women and 38 years (range, 17 to 52) for men.

All patients underwent venous catheterization of the right heart, including the pulmonary artery and the pulmonary arterial wedge position. In addition, 12 had catheterization of the left atrium and left ventricle. The techniques employed in these studies were the same as those previously described[6,7] and were performed by Dr. Earl H. Wood, Dr. H. J. C. Swan, and Dr. John T. Shepherd, with the patients awake and breathing room air. Intravascular pressures were recorded via strain-gauge manometers, the zero reference point being the mid-chest at the third intercostal space with the patient supine. The following formulas were used in calculations:

$$\text{total pulmonary resistance} = \frac{\bar{P}PA \times 1,332}{Q}$$

$$\text{pulmonary vascular resistance} = \frac{[\bar{P}PA - \bar{P}LA] \times 1,332}{Q}$$

In these formulas:

$\bar{P}$ = mean pressure in mm. Hg, measured by planimetry
PA = pulmonary artery
LA = left atrium
Q = the blood flow (cardiac output) in milliliters per second, determined by the Fick principle

In those patients not subjected to left heart catheterization the mean pulmonary arterial wedge pressure was assumed to equal the left atrial pressure.[8-10]

Resistance was calculated in dynes sec. cm.$^{-5}$. Elevated total pulmonary resistance was classified in four gradations: mild (300 to 599 dynes sec. cm.$^{-5}$), moderate (600 to 899), marked (900 to 1,199), and severe (1,200 and more).

Twelve-lead electrocardiograms were obtained in all cases within 2 days of the cardiac catheterization, valvotomy being performed in most cases within the ensuing week.

The ventricular activation times (as derived from the intrinsicoid deflection) and the duration and magnitude of the P, QRS, and T deflections were calculated according to the recommendations of the Committee on Electrocardiography of the American Heart Association.[11] The duration of the complexes and intervals was measured in seconds. The magnitude of the deflections is reported in tenths of a millivolt, the electrocardiograph having been calibrated to the usual sensitivity of 10 millimeters per millivolt.

The electrical axis of the QRS was derived from the algebraic sum of the R and S deflections in Standard Leads I and III, according to the method of Carter and co-workers.[12]

The electrocardiographic categories were defined as previously described[5]: category 1 indicates right bundle branch block of either the partial (QRS = 0.09 to 0.12 sec.) or complete variety (QRS > 0.12 sec.); category 2 is pathognomonic of right ventricular hypertrophy; categories 3 and 4 are suggestive of right ventricular hypertrophy but not diagnostic of it; category 5 is within the range of normal; categories 6A, B, and C represent various degrees of left ventricular hypertrophy; and category 7C is evidence of both left and right ventricular hypertrophy. The presence of partial right bundle branch block was determined from the criteria of Barker and Valencia.[13]

FINDINGS

The principal electrocardiographic and pulmonary vascular measurements were tabulated.* Of the total 80 patients, 46 had sinus rhythm; the remaining 34 had atrial fibrillation. Among the patients with sinus rhythm, the heart rate per minute varied between 46 and 112, averaging 83. Among those with atrial fibrillation, the heart rate per minute ranged between 37 and 112, averaging 70.

*Tables may be obtained from the authors on request.

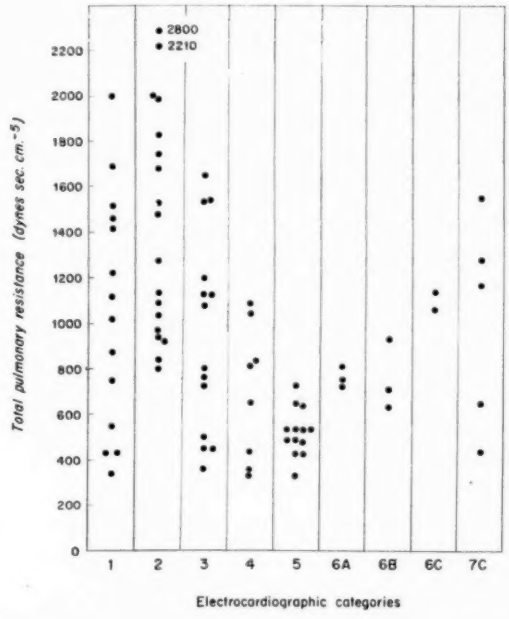

Fig. 1.—Comparison of total pulmonary resistance with electrocardiographic groupings of Pruitt and Robinson[5] in mitral stenosis. See text for description of categories. Each dot represents an individual patient.

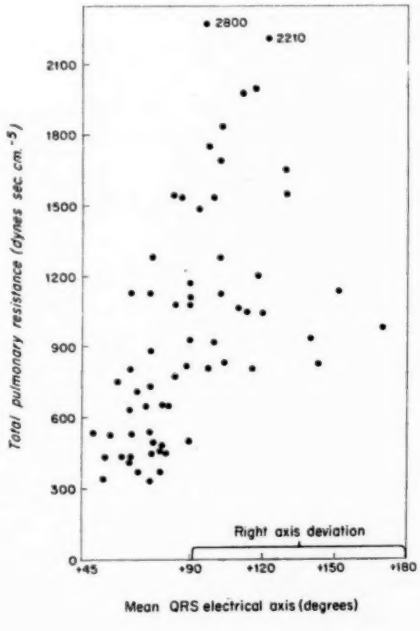

Fig. 2.

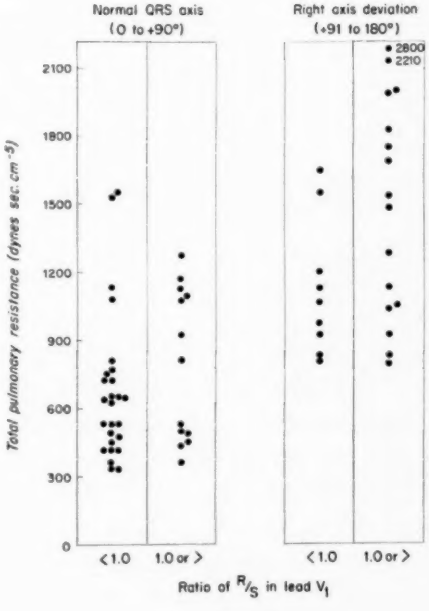

Fig. 3.

Fig. 2.—Comparison of total pulmonary resistance with mean QRS electrical axis in electrocardiograms of patients having mitral stenosis and a QRS of less than 0.08 second's duration. Resistance was 800 or more dynes sec. cm.$^{-5}$ when electrical axis was +91 degrees or greater.

Fig. 3.—Comparison of total pulmonary resistance with ratio of R to S in Precordial Lead V_1 of patients having mitral stenosis and a QRS of less than 0.08 second's duration. Note lack of correlation of pulmonary resistance with R/S ratio in presence of normal axis (*left*), whereas resistance consistently was more than 800 dynes sec. cm.$^{-5}$ regardless of R/S ratio when right axis deviation was present (*right*).

Electrocardiographic Categories.—The relation of the total pulmonary resistance to the individual electrocardiographic categories is depicted in Fig. 1. The wide range in values of the total pulmonary resistance is readily apparent in the group of 14 showing partial or complete right bundle branch block. In this group (category 1) no correlation was identified between electrocardiographic findings and the severity of the pulmonary hypertension. The group showing definite right ventricular hypertrophy (category 2) had moderate to severe pulmonary hypertension, the total pulmonary resistance consistently being elevated to more than 800 dynes sec. cm.$^{-5}$. However, with only suggestive signs of right ventricular hypertrophy (categories 3 and 4), considerable variation was found in the levels of pulmonary resistance. In all patients whose electrocardiograms were within the limits of normal (category 5) the total pulmonary resistance was less than 750 dynes sec. cm.$^{-5}$. When there was electrocardiographic evidence of left ventricular hypertrophy (categories 6A, B, and C and 7C), the level of the pulmonary resistance varied from 435 to 1,550 dynes sec. cm.$^{-5}$, being less than 800 dynes sec. cm.$^{-5}$ in approximately half of this composite group.

Patients With QRS Duration Less Than 0.08 Second.—

Normal axis: Among the 39 cases in which the QRS electrical axis was between 0 and +90 degrees, total pulmonary resistance varied from the mild to the severe gradations (Fig. 2). Hence, in the group with a normal QRS electrical axis, no correlation could be found between the electrocardiographic findings and the degree of obstruction to pulmonary blood flow.

Right axis deviation: The 25 patients with a QRS electrical axis between +91 and +180 degrees all had mean pulmonary arterial pressures ranging from 33 to 89 mm. Hg. Their total pulmonary resistances ranged upward from 800 dynes sec. cm.$^{-5}$, as illustrated in Fig. 2. The pulmonary vascular resistance was greater than 200 dynes sec. cm.$^{-5}$ in 24 of these cases (not available in one).

R/S ratio in Lead V_1: Fig. 3 shows the levels of total pulmonary resistance plotted against the R/S ratio in Lead V_1. It can be seen that in the absence of right axis deviation this ratio was not reliable as a basis for estimating the magnitude of the pulmonary resistance. But in the presence of right axis deviation the total pulmonary resistance was more than 1,000 dynes sec. cm.$^{-5}$ in 80 per cent of the patients having an R/S ratio in Lead V_1 greater than 1.0. The patients with right axis deviation and an R/S ratio in Lead V_1 of more than 1.0 showed a similar marked to severe elevation of mean pulmonary arterial pressure, which was at least 33 mm. Hg in all, and ranged upward from 43 mm. in 80 per cent.

Other Criteria of Right Ventricular Hypertrophy.—The ventricular activation time (intrinsicoid deflection of the QRS) in Lead V_1 was measured in 25 patients. Marked to severe pulmonary hypertension was present in the 12 whose intrinsicoid deflection exceeded 0.04 second in duration. With values less than 0.04 second, considerable variation occurred in the magnitude of the pulmonary resistance. In the other 55 patients, however, the character of the QRS deflection in Lead V_1 made exact measurement impossible and thus reduced the usefulness of this criterion for right ventricular predominance.

T-wave characteristics in the precordial leads were examined in all patients. Inversion of the T waves in Lead V_1 was encountered in association with mean pulmonary arterial pressures varying from 21 to 78 mm. Hg, and total pulmonary resistances varying from 340 to 2,210 dynes sec. cm.$^{-5}$. Upright T waves were found in Lead V_1 in 9 cases in which the total pulmonary resistances ranged from 330 to 1,550 dynes sec. cm.$^{-5}$. In an additional 18 cases the phase of the T waves in Lead V_1 was not discernible. The character of the T waves in Lead V_1, therefore, was of little value in estimating right ventricular stress. However, among 23 patients, inversion of T waves in Lead V_3 was accompanied by total pulmonary resistances in excess of 800 dynes sec. cm.$^{-5}$ in all but one whose electrocardiogram was considered to be within normal range. Except for this helpful inversion of the T wave in Lead V_3, the T-wave changes in Precordial Leads V_1, V_3, and V_5 showed no close correlation with the severity of the pulmonary resistance.

COMMENT

The hazards of predicting hemodynamic states from the electrocardiogram are well recognized. The nature of electrical phenomena associated with the heartbeat should not be interpreted as an immediate and exact reflection of changes in circulatory dynamics or myocardial function. Even so, considerable interest in the correlation of hemodynamic data with the electrocardiogram in congenital and acquired heart disease is demonstrated by the number of recent publications pertaining to this subject.[1,14-26]

In the present study the definitive evidence of right ventricular hypertrophy found in the electrocardiograms of 18 patients (category 2) among the 80 with mitral stenosis was associated uniformly with mean pulmonary arterial pressures of 33 mm. Hg or higher and total pulmonary resistances in excess of 800 dynes sec. cm.$^{-5}$. These results are in essential agreement with those reported by others.[1,20] However, when the signs of right ventricular hypertrophy were only suggestive (categories 3 and 4), the correlation with the severity of the pulmonary hypertension was not so precise. In the group of 22 patients having electrocardiograms suggestive of but not pathognomonic of right ventricular hypertrophy, only 12 had total pulmonary resistances of 800 or more dynes sec. cm.$^{-5}$.

Among the 66 patients having a QRS duration of less than 0.08 second, 25 had a mean QRS electrical axis of +91 or more degrees, and each of these 25 had a total pulmonary resistance of at least 800 dynes sec. cm.$^{-5}$ and a mean pulmonary arterial pressure of 33 or more mm. Hg. This group included all but one of the 18 patients having pathognomonic evidence of right ventricular hypertrophy (category 2), and all but 4 of the 12 patients having only suggestive evidence of right ventricular hypertrophy (categories 3 and 4) and total pulmonary resistances of 800 or more dynes sec. cm.$^{-5}$. Thus, among patients with mitral stenosis the existence of a mean QRS electrical axis of +91 degrees or greater appears to be the most inclusive single index of increased total pulmonary resistance entailing no sacrifice of diagnostic accuracy possessed by any other one electrocardiographic criterion. In line with this, Milnor[4] has written that "the

most important and characteristic electric change produced by right ventricular hypertrophy is the shift of the spatial QRS axis rightward and anteriorly."

It has been said that in older patients, right ventricular hypertrophy infrequently produces frank right axis deviation, the latter being seen more commonly in infancy and childhood.[27] In our patients with mitral stenosis we have found no relation between age and the incidence of right axis deviation as compared with the incidence of normal axis.

Thirteen of our 80 patients had electrocardiograms that were considered to be normal; yet at the time of valvotomy, all were felt to have tight mitral stenosis. It is apparent, therefore, that among patients with mitral stenosis a normal electrocardiogram does not exclude the existence of a severe degree of obstruction at the mitral valve.

Considerable controversy exists as to the significance of an RSR′ complex in Lead V_1 (partial right bundle branch block) in the identification of an increased load of work on the right ventricle.[4,25] Such a finding in the present study bore no quantitative relationship to the pulmonary arterial pressure. Furthermore, in a patient with mitral stenosis having an RSR′ complex in Lead V_1 the electrocardiogram could not be relied upon in precise estimation of the level of the pulmonary vascular resistance.

SUMMARY

Electrocardiograms from 80 adult patients with proved mitral stenosis were correlated with the pulmonary vascular resistances as measured during cardiac catheterization. The finding of a mean QRS electrical axis of +91 or more degrees was the most frequently positive single index of increased total pulmonary resistance among those that entailed no sacrifice of diagnostic accuracy possessed by any other single electrocardiographic criterion. Significant pulmonary hypertension with total pulmonary resistances of more than 800 dynes sec. cm.$^{-5}$ was associated consistently with the electrocardiographic finding of right axis deviation. However, the degree of pulmonary vascular obstruction could not be quantitatively predicted when there was evidence of partial right bundle branch block in Precordial Lead V_1.

We are indebted to Dr. Earl H. Wood, Dr. H. J. C. Swan, and Dr. John T. Shepherd and their co-workers in the cardiovascular laboratory of the Mayo Clinic for their cooperation and for allowing us to review the catheterization data in these cases. We also wish to thank Dr. Howard B. Burchell for his helpful suggestions and pertinent comments.

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Experimental and Laboratory Reports

Bridging of Interrupted A-V Conduction in Experimental Chronic Complete Heart Block By Electronic Means

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The pioneering contribution by Zoll[1,2] on cardiac pacemakers, and the introduction of isoproterenol hydrochloride (Isuprel) in its various forms have significantly influenced the immediate prognosis of patients with complete heart block with asystolic periods (Adams-Stokes syndrome).[3-5] When prolonged management is necessary, the use of external pacemakers is often impractical and the dosage requirements of Isuprel may exceed reasonable amounts and finally may fail altogether. It is our experience that only a few patients are alive 6 to 12 months after the inception of the illness. For the complete heart block developing as a complication during surgery of interventricular septal defects or atrioventricular canals, Lillehei[6] recommended leaving on the surface of the right ventricular wall a braided wire electrode which, together with an indifferent chest-wall electrode, would allow direct cardiac stimulation if necessary. When no longer required it could be withdrawn through the chest without additional intervention. Furthermore, for emergency situations he suggested the percutaneous transthoracic introduction into the right ventricular wall of an electrode wire.[7] With presently available pacemakers the cardiac rate is variable but fixed at any given time. Experiments were undertaken to explore the feasibility of restoring atrioventricular conduction, providing thus the cardiac dynamics with autonomic control which for all practical purposes is only mediated through the sinus node: bradycardia with rest, tachycardia with a demand for increased cardiac output. An analysis of the factors to be encountered made us postulate that such an electronic pacemaker could be developed if it utilized the patient's atrial complex to trigger a stimulator unit. We therefore directed our attention

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predominantly toward the technical parameters necessary to accomplish atrioventricular conduction dependably, to design electrodes and electronic gear, and to test such a device in animals. The eventual purpose is its application in human beings with chronic complete heart block and asystolic periods, and with this aim in mind, a compact and transistorized unit is presently being built.

The present report merely enumerates some observations of successful re-establishment in dogs of atrioventricular conduction by electronic means.

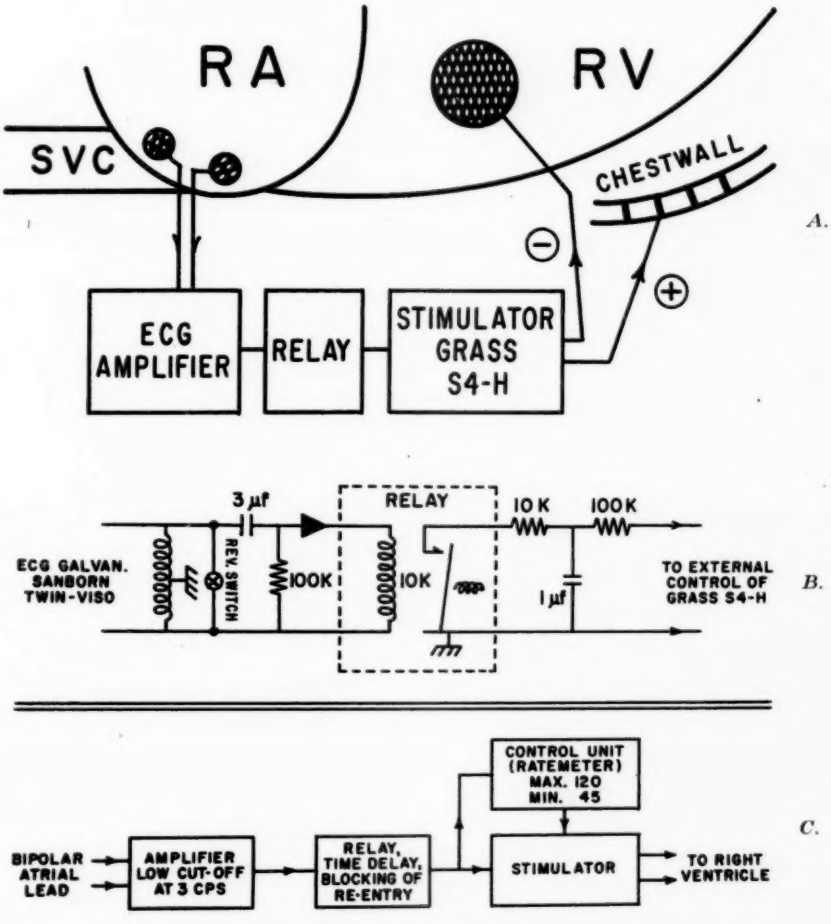

Fig. 1.—*A*, Block diagram of electronic atrioventricular bridge as used in our experiments. *B*, Circuit diagram of connecting atrial bipolar complexes through relay to Grass S4-E physiologic stimulator. *C*, Block diagram: A-V bridge for application in human beings.

METHODS

Surgical Procedure.—Four mongrel dogs in good health, weighing 15 to 24 kilograms, were used in this study. Following anesthesia with sodium Nembutal (25 to 30 mg./Kg. of body weight), a right thoracotomy in the fifth intercostal space was performed under sterile conditions. An endotracheal tube connected to an automatic respirator utilizing compressed air was employed to maintain controlled respirations.

The azygos vein was ligated with a single 3-O silk ligature, and umbilical tapes were placed about the superior and inferior venae cavae in preparation for a period of complete occlusion of

the cardiac inflow. The pericardium was opened and the heart marsupialized by suture of the pericardial edges to the chest wall. The Mount Sinai atriotomy clamp[8] was next sutured in place on the wall of the right atrium. The wall between the jaws of the clamp was next incised, the cavae occluded, the clamp opened, and the atrium entered. A single 2-O silk suture was then inserted through the septal leaflet of the tricuspid valve at right angles to the annulus of the valve. The suture emerged through the interatrial septum and was tied tightly in place across

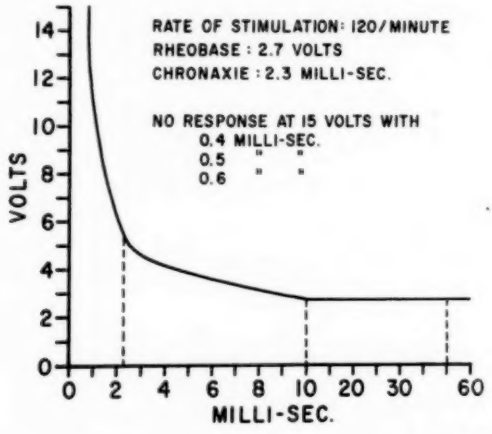
RATE OF STIMULATION: 120/MINUTE
RHEOBASE : 2.7 VOLTS
CHRONAXIE : 2.3 MILLI-SEC.
NO RESPONSE AT 15 VOLTS WITH
0.4 MILLI-SEC.
0.5 " "
0.6 " "
VOLTS
0 2 4 6 8 10 12 14
0 2 4 6 8 10 20 30 60
MILLI-SEC.

Fig. 2.—Composite curve of several determinations of rheobase and chronaxie. It is evident that stimulating pulses should be of more than 2 milliseconds in duration and no less than 3 volts (with voltage the variable).

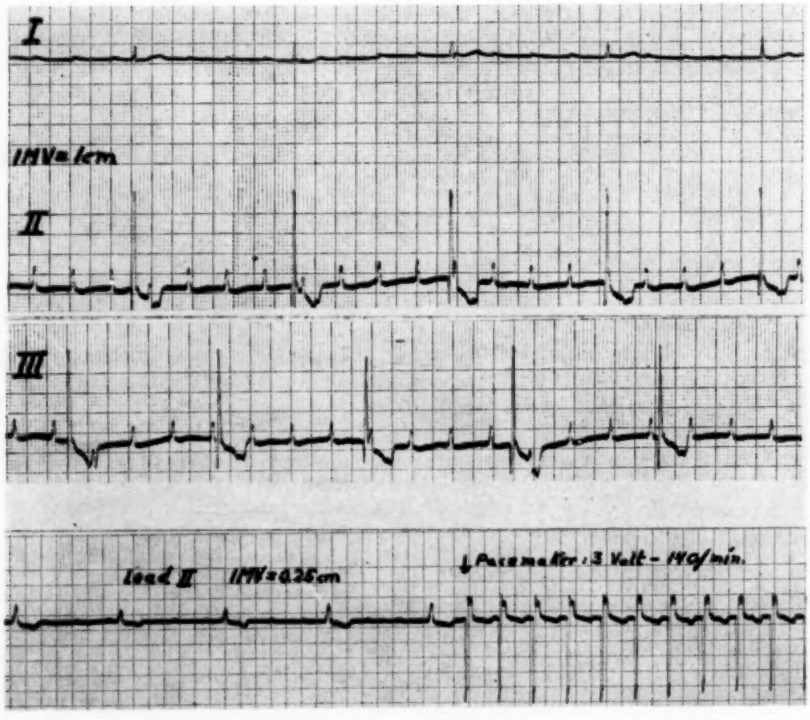

Fig. 3.—Chronic complete heart block in dogs. The lowermost part of the illustration shows the instantaneous response to the stimulator, 140 beats per minute and 4 milliseconds in duration (paper speed 25 mm./sec.).

the annulus. The suture was placed approximately 1 to 1.5 cm. anterior to the coronary sinus orifice. The occluding tapes were next released, allowing blood to enter the atrium and displace air. The jaws of the clamp were then closed, thus closing the atrium. The atrial incision was closed with a continuous 4-O silk suture.

Two circular tantalum mesh electrodes were next sutured onto the external surface of the right atrium close to its junction with the superior vena cava. A third such electrode was sutured onto the right ventricular wall (Fig. 1,*A*). The wires interwoven in the electrodes and insulated through polyethylene tubing were brought out through the chest incision. Another wire used as the indifferent electrode was sutured in place in the subcutaneous tissue of the wound.

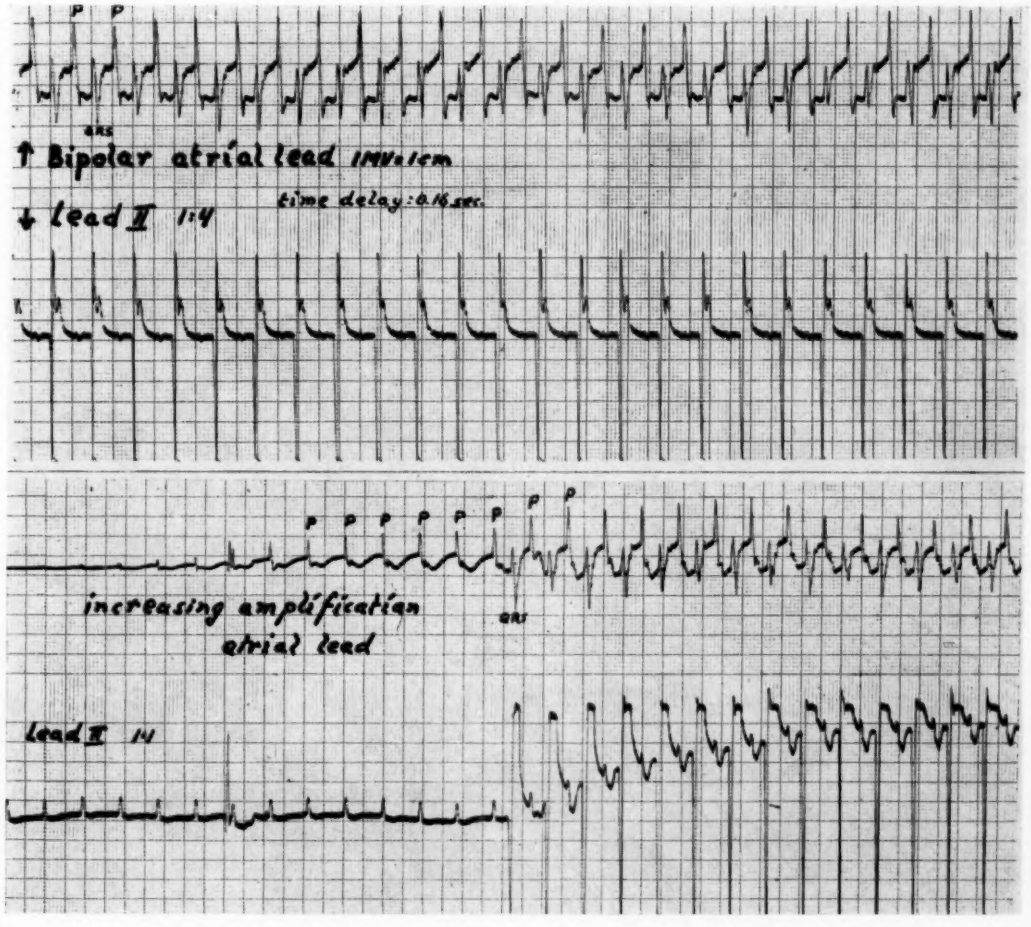

Fig. 4.—The bipolar atrial lead is used to trip the stimulator, which responds with a pre-set time delay of 0.16 second (3 volts, 4 milliseconds, 25 mm./sec. paper speed). The tracing below demonstrates the dependence upon an adequate trip voltage and the independence of the stimulator voltage from the amplitude of the atrial complex.

Technique of A-V Bridging.—Bipolar atrial complexes were fed into one channel of the Sanborn Twin-Viso, which can amplify 1 millivolt at the input to 30 volts across the outer ends of the center-tapped galvanometer coil. The amplified atrial complexes were used to energize a relay through a blocking condenser. A polarity reversal switch at the input and rectifier allow selection of the phase of the deflection for tripping the relay. The latter, in turn, discharges to ground the condenser of an RC circuit bridging the "external control" terminals of a Grass Model S-4E physiologic stimulator. This condenser blocks the entry of further trip voltages from above

(atria) for 0.1 to 0.15 second and prevents self-sustained oscillation between atria and ventricles by blocking the re-entry (feedback) of the ventricular response. A series resistor limits the condenser discharge current and protects the relay contacts (Fig. 1,*B*).

Electrodes.—The electrodes were cut from tantalum mesh, about 10 mm. in diameter for the atria and about 15 mm. for the ventricle. Braided stainless steel wire was woven into the electrodes. Polyethylene tubing was slipped over the wire up to the electrodes. Attachment of electrode assembly to patches of synthetic material (Dacron, Ivalon) may expedite their application to the myocardial surface in human beings.

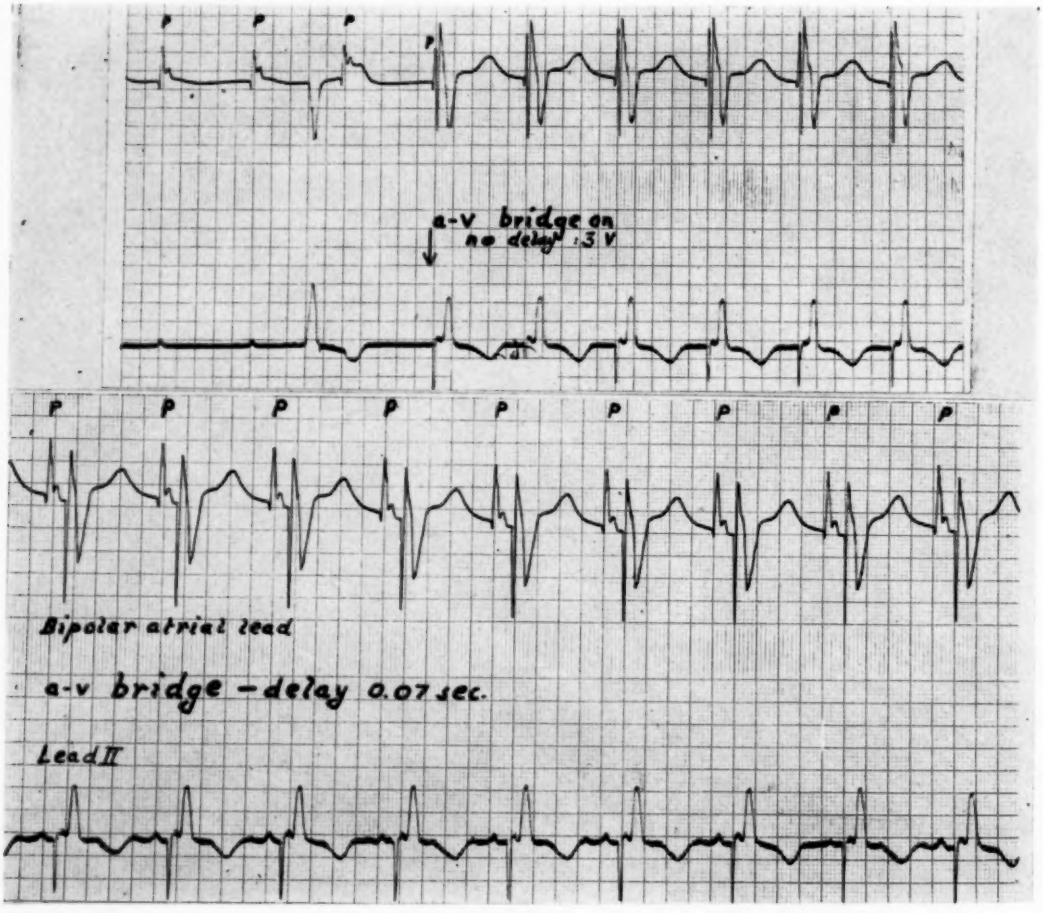

Fig. 5.—Upper tracing: bipolar atrial lead and Lead II. At the point indicated by the arrow the A-V bridge is turned on, with instantaneous response (3 volts, 4 milliseconds, no delay, 50 mm./sec. paper speed). Lower tracing: A-V bridge with time delay of 0.07 second.

Stimulating voltage: All experiments were performed when recovery from surgery was complete, and without anesthesia. Determinations of rheobase and chronaxie were made with the stimulator set at a fixed rate of 120 per minute. A composite from numerous determinations is shown in Fig. 2. This correlates well with the data of Frooks and collaborators.[9] Three to eight volts with a square wave duration of 4 milliseconds were found most satisfactory for consistent stimulation (Fig. 3). The higher voltages appeared to be necessary when heart failure prevailed. Varying the time delay between the trip voltage (amplified atrial complex) and the discharge of the stimulus allows stimulation with physiologic delay of stimulus propagation through the A-V node (Figs. 4, 5, 6). If the time delay chosen exceeded the P-P interval, stimulation occurred at a 2:1 ratio.

In an experiment not basically related the QRS complex was used to trip the relay-stimulator array. By choosing an appropriate time delay, a self-cycling oscillating relationship was achieved, to which "tuning in" was achieved through variation of the time delay between tripping of relay and stimulation.

Experimental Asystolic Periods (Adams-Stokes Seizures).—Turning off the stimulator produced asystolic periods, Adams-Stokes seizures, clinically. The atrial mechanism continued with a long ventricular asystole, delayed emergence of an idioventricular focus which was irregular and slow and required considerable time to settle down to a regular idioventricular rhythm (Fig. 7*A*). The dog would meanwhile become unresponsive. Turning on the stimulator would abolish the asystole and Adams-Stokes attack at once (Fig. 7*B*). Pressure recordings demonstrated an instantaneous return of pressure and pulse contour (obtained through retrograde catheterization of the ascending aorta).

Experimental Prevention of Asystolic Periods.—As has been shown, the sudden turning off of the stimulator when driving ventricles at a steady rate of 120 per minute will result in an asystolic period. When, however, the stimulating rate was gradually diminished close to the rate of the idioventricular focus, the sudden turning off of the stimulator resulted in an immediate take-over of the idioventricular focus (Fig. 8*A*).

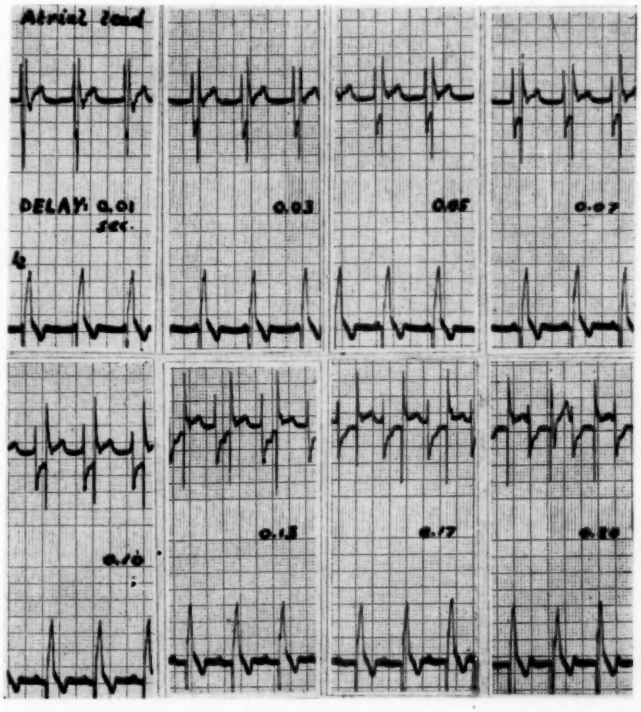

Fig. 6.—The effect of time delays of 0.01 to 0.20 second are shown.

Isoproterenol Hydrochloride (Isuprel).—Isuprel, 0.1 mg. given intramuscularly, also prevented asystolic periods upon sudden stopping of the stimulator (Fig. 8*B*). One hour afterward, only a very slight diminution of the protective action was noticeable. It seems apparent that isoproterenol hydrochloride produces an alert ready-state of the idioventricular focus, ready to assure instantaneous response upon failure of higher pacemakers to "drive" the heart. This we regard as its principal action in preventing the occurrence of asystolic periods. The well-known "speeding up" property upon the idioventricular rate will improve the cardiac dynamics (minute volume, mean pressure).

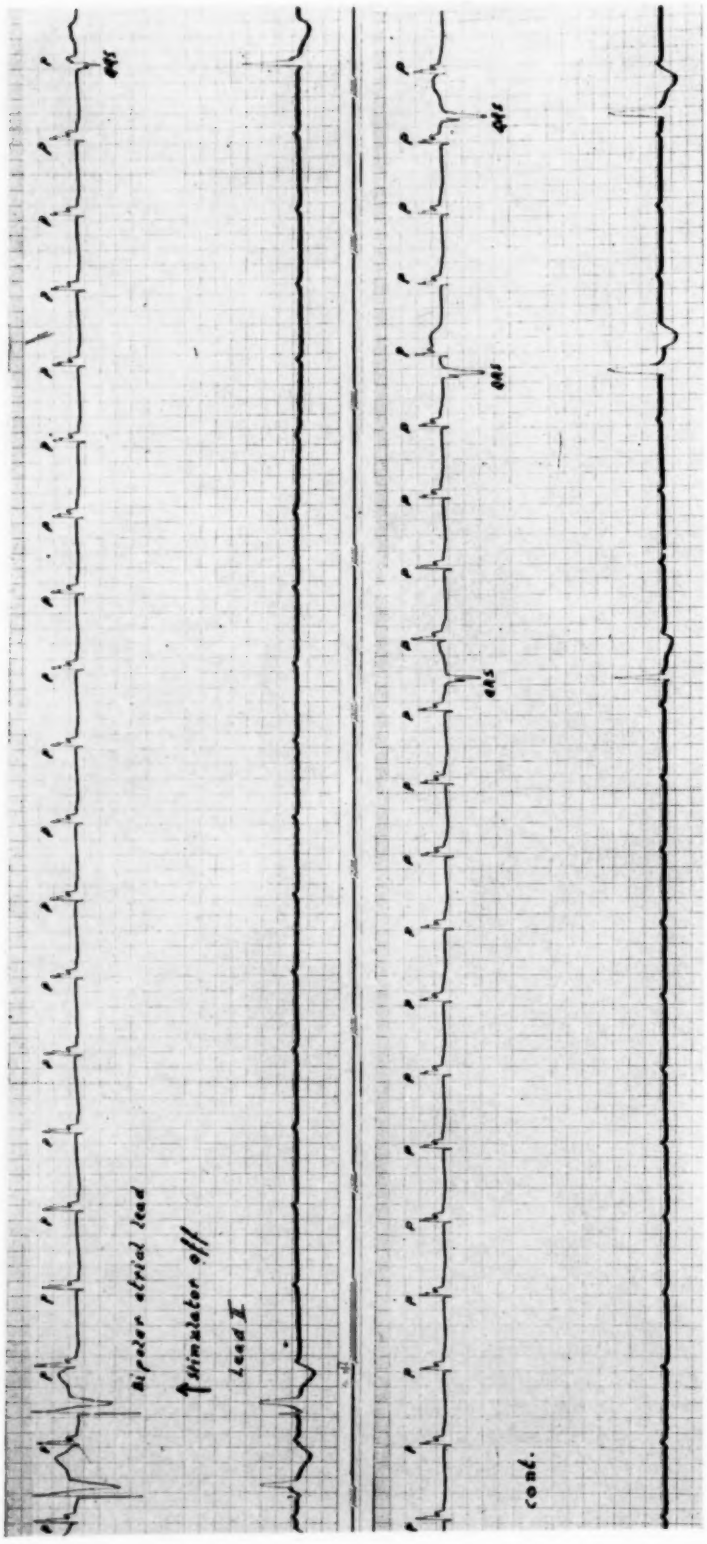

Fig. 7A.—Continuous tracing. At the point indicated by the arrow the stimulation is turned off, followed by prolonged ventricular asystole (paper speed, 50 mm./sec.).

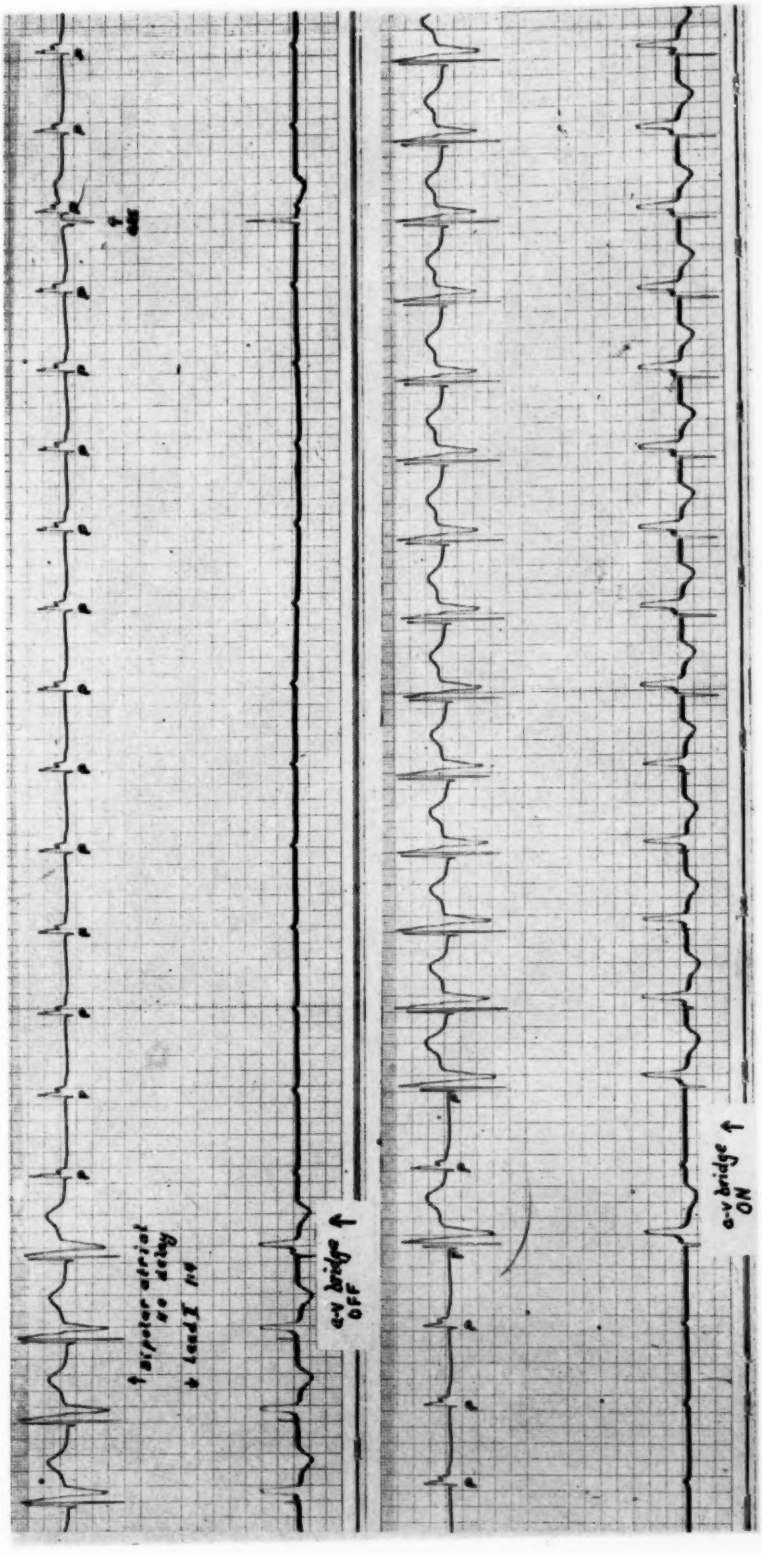

Fig. 7B.—Turning on stimulator results in instantaneous response of the ventricles.

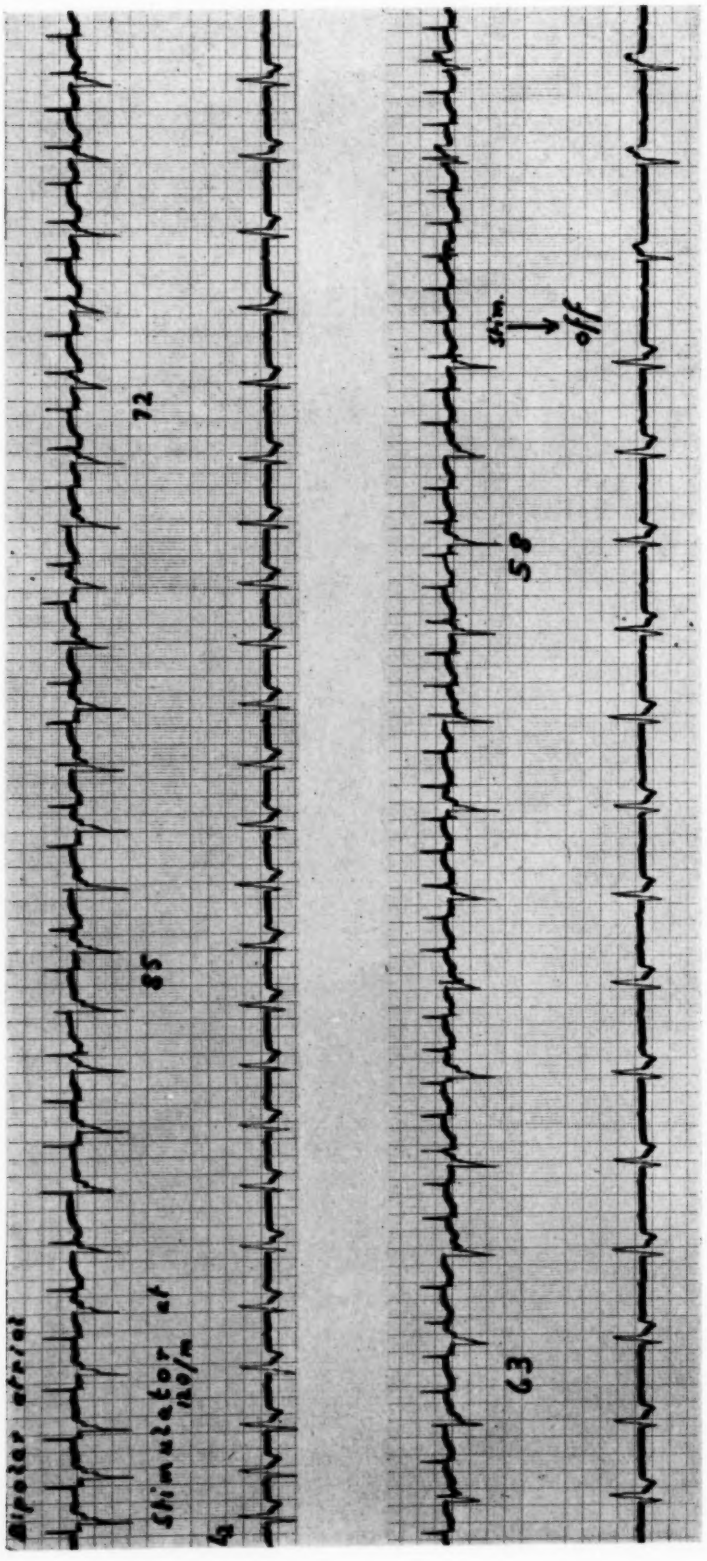

Fig. 8.A.—With the stimulator gradually being turned down from 120 beats per minute toward the rate of the idioventricular focus results in its instantaneous response once the stimulator is turned off, without asystolic periods.

Experimental Production of Reversible Congestive Heart Failure.—As has been shown by Starz[1] and Gaertner,[10] dogs with chronic complete heart block will develop congestive heart failure: within 1 to 2 weeks the animals develop pulmonary congestion, hydrothorax, ascites, etc., and become very apathetic. In our experiments, when a normal ventricular rate was restored either by electronic re-establishment of A-V conduction or direct stimulation at a rate of 120 per minute, a marked diuresis ensued, with disappearance of all signs of heart failure. The reversibility of the heart failure without the action of any drug appears to be an interesting avenue to the study of the numerous facets of congestive heart failure.

Apparatus: Design for Application in Human Beings.—On the basis of the experience from our experiments, a compact transistorized battery-operated unit is being built, encompassing an atrial complex amplifier, suitable filters, a time delay of 0.15 second, and adequate milliampere voltage control. A safety device is incorporated: should the atrial rate exceed 120 or fall below 45, the stimulator will automatically be driven at a fixed rate of 75 per minute.

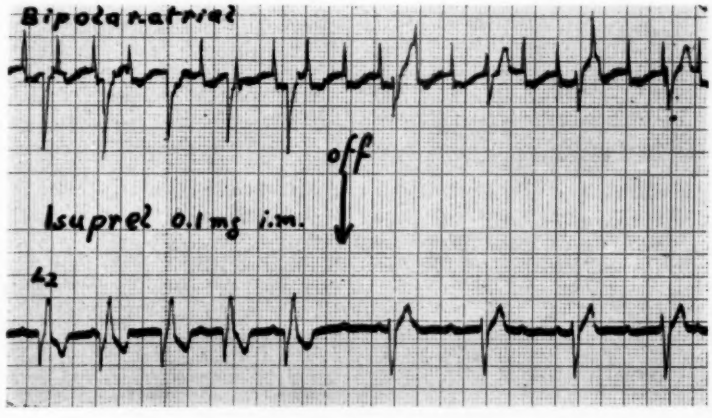

Fig. 8*B*.—Isuprel given intramuscularly produces similarly instantaneous response of the idioventricular focus when the stimulator is turned off, thus preventing asystolic episodes.

DISCUSSION

At the present time electrical stimulation of the ventricular myocardium can be accomplished by one of three methods: (a) external electrical stimulation as described by Zoll and associates[1,2]; (b) direct implantation of an electrode wire into the myocardium, either under direct vision or percutaneously (Lillehei and associates[6,7]); (c) placement of an intracardiac catheter electrode by the venous route (Furman and Robinson[11]).

In all of these techniques a pacemaker delivering a fixed rate of stimulation is employed. Such an approach has not only proved to be a temporary lifesaving measure but in occasional instances has been shown to provide reliable stimulation for months. For a long-range maintenance of stimulation it would be advantageous to have a pacemaker which automatically responds by increasing the stimulation rate during periods of increased demand, such as exercise, and automatically slows during periods of decreased demand, such as rest. In complete heart block the atria, being controlled by the sinoatrial node, respond normally to autonomic stimuli. Re-establishment of atrioventricular conduction would appear therefore to be the most physiologic approach. In the past, Aixala and co-workers,[12] by means of a muscular atrioventricular bridge, attempted to re-

establish atrioventricular conduction in cases of complete heart block in dogs. Since all attempts were made in acute experiments, spontaneous return of A-V conduction cannot be excluded. Bailey's[13] report of a surgical attempt in a 36-year-old patient with chronic rheumatic heart disease does not suggest that it resulted in normalization of A-V conduction, which occurred only 6 days later, the ventricular complexes never having been of idioventricular configuration. Critical appraisal of the electrical requirements precludes success of a muscular bridge in either dogs or human beings. Butterworth and Poindexter,[14] in essence, used an electronic A-V bridge in their experimental attempts to reproduce Wolff-Parkinson-White type of QRS complexes: the atrial complexes, amplified several thousand times, were used to stimulate the right ventricle directly. Folkman and Watkins[15] employed the same technique in experimental complete heart block. In such an arrangement the stimulating voltage would depend on, and vary with, the amplitude of the atrial complexes. It is apparent that to use the atrial complex voltage only to trip a separate stimulator is more dependable. This has been accomplished with the equipment and techniques described in this paper. The use of induction devices would allow radio control and closed-chest procedures.[16] Although applicable to experimental conditions the technical obstacles for the development of such a unit for human beings appear great.

Chronic complete blocking of the heart is a good technique for producing heart failure in dogs; such heart failure is reversible when normal ventricular rate is restored.

CONCLUSIONS

1. Electronic re-establishment of atrioventricular conduction has been accomplished.

2. Rheobase and chronaxie of the ventricular myocardium have been determined.

3. Asystolic periods (Adams-Stokes seizures) have been experimentally reproduced.

4. Asystolic periods could be prevented by gradual slowing of the pacemaker down to the rate of the idioventricular focus. This appears to be significant in the handling of the pacemaker in clinical cases in the "weaning off" period.

5. Isoproterenol hydrochloride (Isuprel) stimulated the idioventricular focus into a more sensitive "ready state" to take over at once upon failure of higher pacemakers to drive the heart. This is regarded as the principal action of Isuprel in preventing asystolic attacks.

6. Reversible heart failure has been produced experimentally through the combination of complete heart block and chronic implantation of stimulating electrodes.

7. Based upon the accumulated experimental data an instrument is under construction which is applicable to human beings. The poor prognosis of patients with chronic complete heart block and asystolic periods requires that such patients be provided with implanted electrodes for electronic re-establishment of A-V conduction and cardiac stimulation.

We wish to express our deep appreciation to Dr. Ivan D. Baronofsky, Director, Department of Surgery, for his generous assistance and advice.

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The Systolic J-M Stroke Displacement and Gram-Centimeters Values of Fifty-One Normal Males From An ULF Pendulum Ballistocardiographic System

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The general trend of various workers to employ ultralow-frequency[1] ballistocardiographic systems has created the need "to describe new criteria of normals varying with age,"[2] as well as to determine results in abnormal and pathologic conditions.

The ultralow-frequency displacement ballistocardiogram is in essence the whole body plethysmogram,[3] representing the temporal algebraic summation of the plethysmogram (full cardiac cycle) of larger arteries ("down to an internal diameter of 1.1 mm.")[4] in relation to their distance from the heart. The predicted[4] amplitudes (quantitative values) and wave form of the displacement, velocity, and acceleration functions of the ultralow-frequency ballistocardiogram by this method of analysis are comparable to experimental[5] results.

With the determination of quantitative platform displacement values, an empiric "body + platform" Mass · Displacement value may be calculated. This value M · D, Gm.-cm.) is theoretically equivalent to the internal cardiovascular mass · displacement value resulting from periodic displacement of the internal center of gravity of the body with each contraction of the heart and flow of blood in the greater vessels. The degree of correlation of these values yet remains to be determined, however.

The platform displacement curve is the external recoil record of this internal mass displacement, and if inverted (in reference to normal platform polarity; headward = upward, and footward = downward, graph deflection) it indicates the actual direction of the central cardiovascular mass movement.

Initial studies on 12 subjects[5] have been extended to 51 normal males and constitute the present report.

METHOD

The system used in this study has been described previously.[4] The natural cycle frequency of the system was 0.5/sec., with a calculated response range from 0.2/sec. (F-1) to 12.0/sec. (F-2). The damping was weak, i.e., 0.28 critical.

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The transducer was a calibrated integrating coil-magnet velocity meter.[6a-b] The recorder was a single- or double-channel Sanborn direct-writing electrocardiograph.

All subjects were normal by cardiac auscultation, blood pressure determination, and chest x-ray for cardiac size. They had not eaten or smoked for 2 hours prior to the recordings. Attainment of a basal state was not attempted, since prior observations had revealed deterioration of the ballistocardiogram with prolonged recumbency on the ballistic platform. Records were made during held maximal expiration and held maximal inspiration. The room environment was air-conditioned (year-round), and the temperature was thermostatically controlled (78°F.).

Direct measurements of the J-M stroke displacement value (calibration, 1.0 millivolt output = 0.005 cm.) were made on expiratory and inspiratory records of a stable pattern from complex to complex. The Mass · Displacement (Gm.-cm.) was calculated for expiration and inspiration. The Mass factor was the "body plus platform" weight.

DISCUSSION

A displacement (expiration, *A-1*, and inspiration, *A-2*) record* of a normal subject is shown in Fig. 1. Fig. 2 shows the frequency distribution of subject data, with one standard deviation for age (*A*, years), height (*B*, cm.), body surface area (*C*, M.²), and "body plus platform" weight (*D*, Kg.). Fig. 3 shows

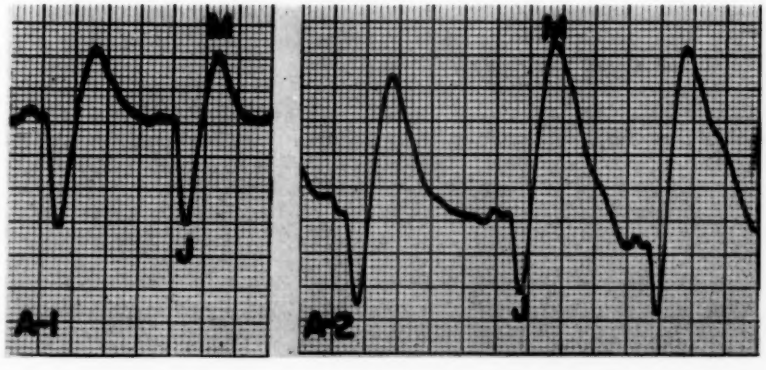

Fig. 1.—Displacement record of normal male subject: age, 22 years; height, 72 inches; weight, 145 pounds. Calibration, 12 small vertical chart spaces (millimeters) = 1.0 mv. = 0.005 cm. *A-1*, Expiration J-M = 25/12 × 0.005 = 0.0104 cm. *A-2*, Inspiration J-M = 38/12 × 0.005 = 0.0158 cm.

the frequency distribution, with one standard deviation, of expiratory J-M displacement (*A*, microns) and calculated M · D value (*B*, Gm.-cm.); the inspiratory J-M displacement (*C*, microns) and calculated M · D value (*D*, Gm.-cm.). For purposes of graphing, the displacement values in *A* and *C* have been converted (Table 1, J-M values in cm.) to microns (1.0 micron = 0.0001 cm.). Only 44 inspiratory values (*C* and *D*) are present.

There are a few published ultralow-frequency displacement values for comparison with the values in this report. An earlier study[5] on 12 subjects using

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***Complete subject and platform data with displacement (cm.) and moment (Gm.-cm.) values are given in a table which has been deposited as Document Number 6106 with the ADI Auxiliary Publications Project, Photoduplication Service, Library of Congress, Washington 25, D. C. A copy may be secured by citing the document number and by remitting $1.25 for photoprints, or $1.25 for 35 mm. microfilm. Advance payment is required. Make checks or money orders payable to: Chief, Photoduplication Service, Library of Congress.**

a ball-bearing and Nickerson-type ULF system gave an average J-M displacement value of 86.5 microns. In the same study, using the pendulum system described herein (*METHOD*), the average J-M value on the same 12 subjects was 113 microns.

A recent report[3] on results obtained with a differential pendulum* has appeared. The mean J-M (25 males, 20 to 29 years of age) was 92.8 microns, and the J-M Mass · Displacement value was 763.7 Gm.-cm.

The average J-M displacement value in this study may be calculated as follows in order to correct for the difference between the number of expiration and inspiration samples, i.e.:

$$\frac{(51 \times 100.8) + (44 \times 126)}{51 + 44} = 112.5 \text{ microns}$$

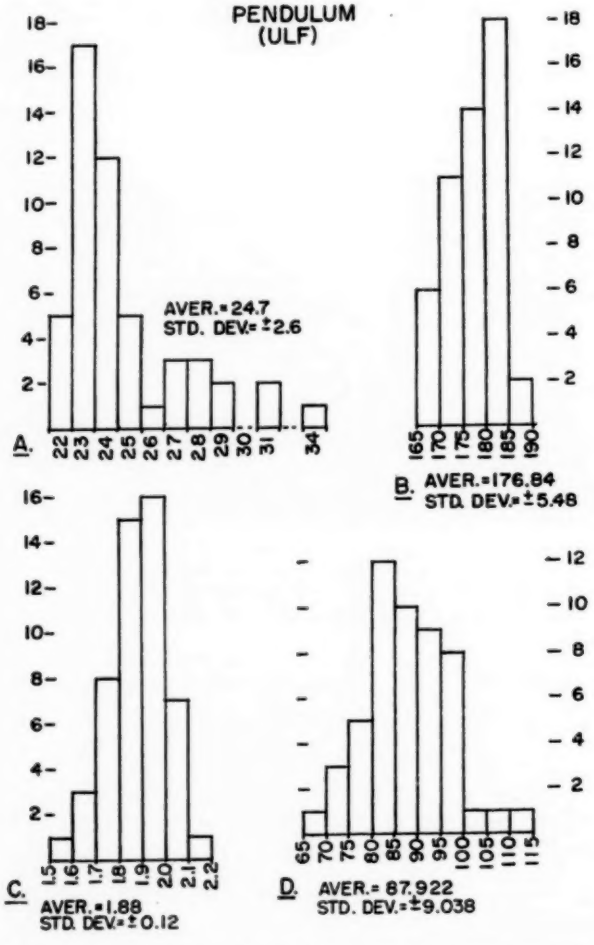

Fig. 2.—Bar-frequency diagrams showing number of subjects with average and 1 standard deviation for: *A*, age in years; *B*, height in centimeters (group units of 5 cm.); *C*, body surface area in square meters (group units of 0.1 $M.^2$); *D*, combined weight factor, body plus platform, in kilograms (group units of 5 Kg.).

*This system combines a simple positive pendulum (wire suspension) with an inverted pendulum support (dural tubing), with the details of construction being given in the Appendix of an article by Scarborough, et al.[3]

The average J-M Gm.-cm. value for this study is also calculated as follows, i.e.:

$$\frac{(51 \times 883.82) + (44 \times 1108.83)}{51 + 44} = 988.03 \text{ Gm.-cm.}$$

These values exceed those of the differential pendulum, respectively, by 19.7 microns and 224.33 Gm.-cm. It is noteworthy that the displacement value for the 51 subjects (112.5 microns) is practically the same as was obtained in the earlier study[5] on 12 subjects (113 microns), using the same pendulum system.

It is of interest to compare the values of the present study with those of Henderson's original work.[7] From his Dh (J-M) values* on 8 subjects (20 to 28 years of age) the following results are obtained after determining the uncorrected Dh (J-M) value for each subject: (1) average uncorrected Dh (J-M) value of 94.3 microns, and (2) average Gm.-cm. value of 727.29 (average body plus platform weight factor equals 77.125 Kg.)

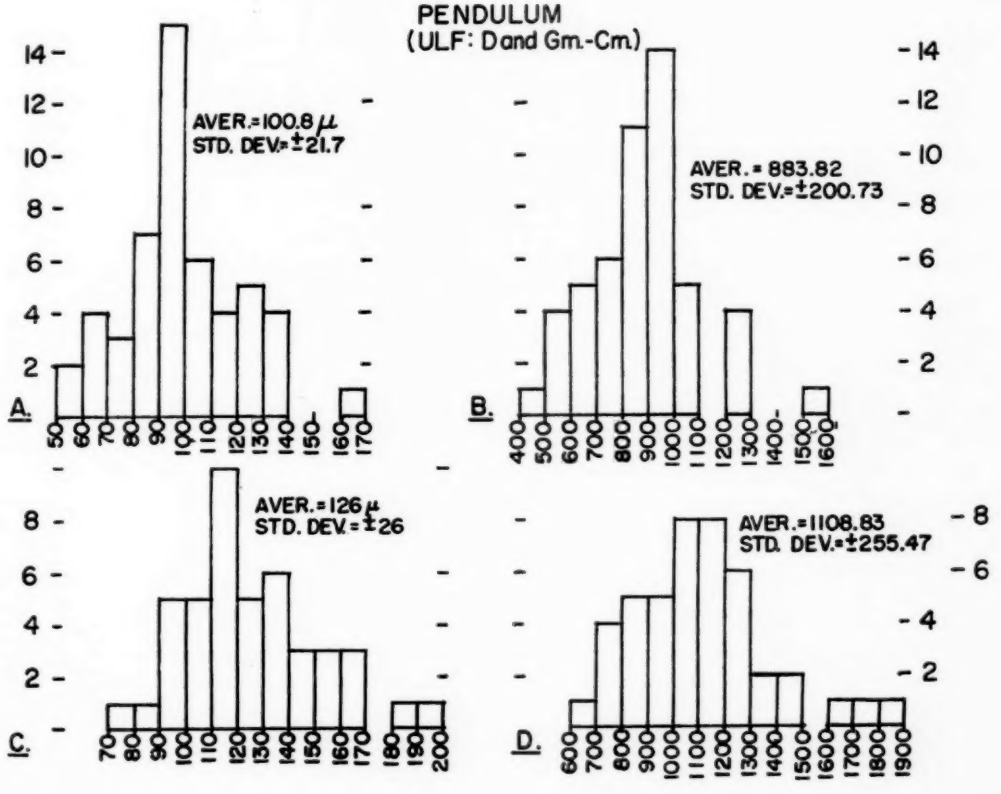

Fig. 3.—Bar-frequency diagrams showing number of subjects with average and 1 standard deviation for: *A*, expiratory J-M displacement in group units of 10 microns (average = 100.8; standard deviation = ±21.7); *B*, expiratory J-M Gm.-cm. value in group units of 100 Gm.-cm. (883.82; ±200.73); *C*, inspiratory J-M displacement in group units of 10 microns (126; ±26); *D*, inspiratory J-M Gm.-cm. value in group units of 100 Gm.-cm. (1108.83; ±255.47). Displacement values (cm.) in Table 1 have been converted to microns (0.0100 cm. = 100 microns) for graphing purposes.

*Henderson's values were corrected for platform weight, i.e., "body plus platform weight/body weight" multiplied by measured amplitude equals corrected amplitude. This correction was eliminated in order to compare his values with those of the present study.

a ball-bearing and Nickerson-type ULF system gave an average J-M displacement value of 86.5 microns. In the same study, using the pendulum system described herein (*METHOD*), the average J-M value on the same 12 subjects was 113 microns.

A recent report[3] on results obtained with a differential pendulum* has appeared. The mean J-M (25 males, 20 to 29 years of age) was 92.8 microns, and the J-M Mass · Displacement value was 763.7 Gm.-cm.

The average J-M displacement value in this study may be calculated as follows in order to correct for the difference between the number of expiration and inspiration samples, i.e.:

$$\frac{(51 \times 100.8) + (44 \times 126)}{51 + 44} = 112.5 \text{ microns}$$

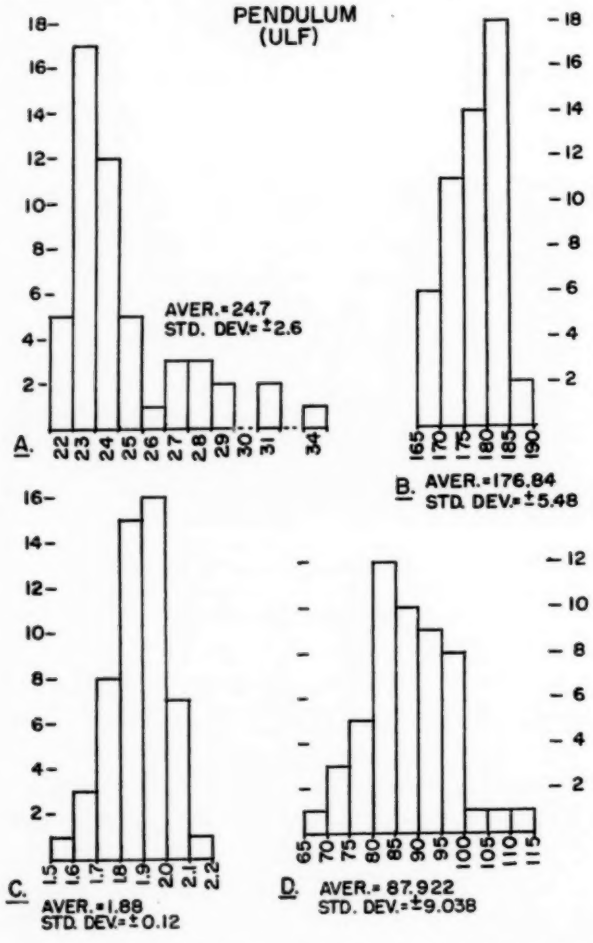

Fig. 2.—Bar-frequency diagrams showing number of subjects with average and 1 standard deviation for: *A*, age in years; *B*, height in centimeters (group units of 5 cm.); *C*, body surface area in square meters (group units of 0.1 M.^{2}); *D*, combined weight factor, body plus platform, in kilograms (group units of 5 Kg.).

*This system combines a simple positive pendulum (wire suspension) with an inverted pendulum support (dural tubing), with the details of construction being given in the Appendix of an article by Scarborough, et al.[3]

The average J-M Gm.-cm. value for this study is also calculated as follows, i.e.:

$$\frac{(51 \times 883.82) + (44 \times 1108.83)}{51 + 44} = 988.03 \text{ Gm.-cm.}$$

These values exceed those of the differential pendulum, respectively, by 19.7 microns and 224.33 Gm.-cm. It is noteworthy that the displacement value for the 51 subjects (112.5 microns) is practically the same as was obtained in the earlier study[5] on 12 subjects (113 microns), using the same pendulum system.

It is of interest to compare the values of the present study with those of Henderson's original work.[7] From his Dh (J-M) values* on 8 subjects (20 to 28 years of age) the following results are obtained after determining the uncorrected Dh (J-M) value for each subject: (1) average uncorrected Dh (J-M) value of 94.3 microns, and (2) average Gm.-cm. value of 727.29 (average body plus platform weight factor equals 77.125 Kg.)

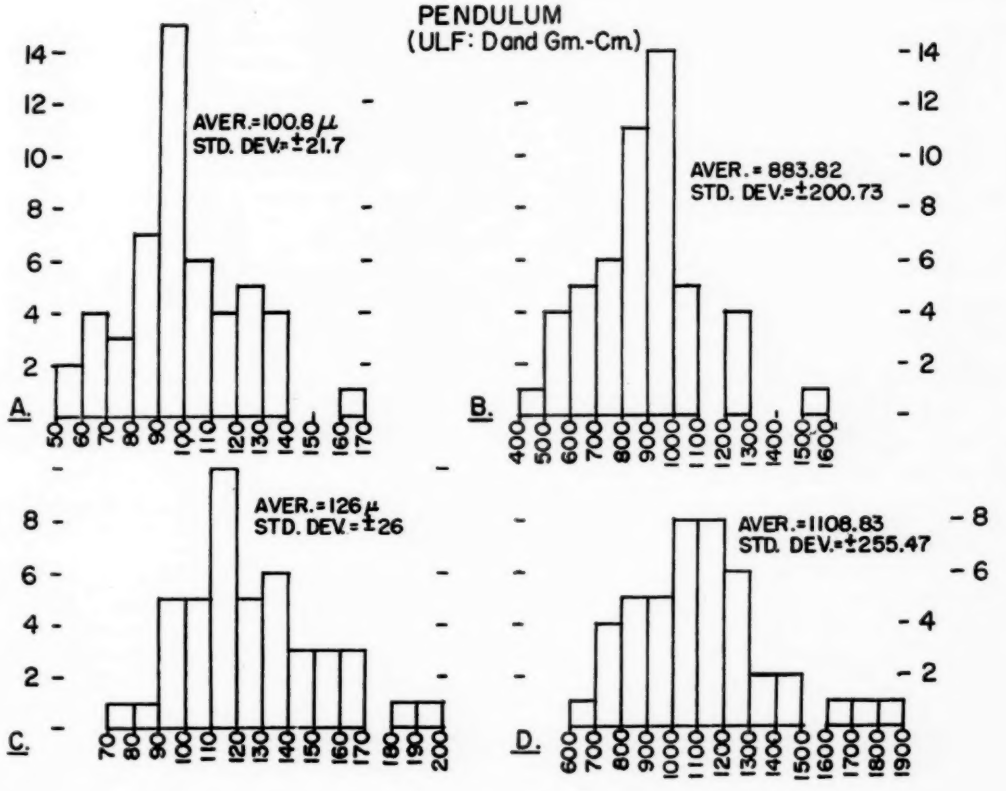

Fig. 3.—Bar-frequency diagrams showing number of subjects with average and 1 standard deviation for: *A*, expiratory J-M displacement in group units of 10 microns (average = 100.8; standard deviation = ±21.7); *B*, expiratory J-M Gm.-cm. value in group units of 100 Gm.-cm. (883.82; ±200.73); *C*, inspiratory J-M displacement in group units of 10 microns (126; ±26); *D*, inspiratory J-M Gm.-cm. value in group units of 100 Gm.-cm. (1108.83; ±255.47). Displacement values (cm.) in Table 1 have been converted to microns (0.0100 cm. = 100 microns) for graphing purposes.

*Henderson's values were corrected for platform weight, i.e., "body plus platform weight/body weight" multiplied by measured amplitude equals corrected amplitude. This correction was eliminated in order to compare his values with those of the present study.

The values (J-M displacement and Gm.-cm.) of the present study are found, therefore, to exceed published values of other normal studies using the ultralow-frequency ballistocardiographic method.

SUMMARY

1. The J-M displacement and Mass · Displacement values of 51 normal male subjects from an ultralow frequency pendulum ballistocardiographic system have been given.

2. These values exceed those of previous studies.

3. The ballistocardiographic Mass · Displacement value thus obtained is related to the internal cardiovascular mass · displacement value. Their degree of correlation remains to be established, particularly in regards to equating the internal cardiovascular mass and displacement values individually.

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High Anterior Precordial Lead Studies. I. Techniques and Normals

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The significance and value of the precordial leads have long been of interest to cardiologists and physiologists. Since 1938, the method of recording leads has been relatively standardized. This is the result of a Committee Report which represented the attitudes of the American Heart Association and the Heart Association of Great Britain and Ireland.[1]

Cardiologists and physiologists have long been aware that precordial leads placed strictly in the standard positions in many instances do not reveal or show the true cardiac picture. Many text books and laboratory guides indicate this situation and suggest moving the exploring chest electrode to various positions under certain circumstances. Burch and Winsor[2] state that "there is a greater need to consider the term exploring electrode literally and actually to explore the various regions of the heart in order to locate precisely the site of infarction and to estimate its size. When infarction is suggested, search should be made from area to area until the surface of the heart has been explored thoroughly." Prinzmetal, Kennamer and Massumi[3] in their studies of high anterior myocardial infarction utilized this principle in making electrocardiographic studies in individuals of 40 years of age and over.

METHODS

Believing that the upper chest area holds potentially valuable diagnostic information, we undertook the current project in order to record the normal complexes derived from the upper chest area. To obtain this information the series of new multiple chest leads described in this paper were made on hundreds of young male and female college students. From this group, the records of 50 young men and 50 young women in good health and with normal ECG records in the twelve leads usually recorded were used for this study. The young men ranged in age from 16 to to 29 years and averaged 21½ years. The young women ranged in age from 16 to 21 years and averaged just slightly over 19 years of age.

This study, after many trials and checks, was based on the routine use of the electrocardiographic technique described as follows:

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A. Standard: I, II, III
B. Leads aVR, aVL, aVF
C. Chest Leads V_1-V_6
D. Supplementary Precordial Electrode Positions

The leads in A, B, C were used routinely to determine electrical position and normality (Figs. 1, 2, 3). Five electrode positions were used at the sternal level of the second intercostal space directly above the conventional positions V_1 through V_5, and six electrode positions were employed directly above positions V_1 through V_6 at the sternal level of the third, fourth, and fifth intercostal spaces. Lepeschkin's terminology[4] was followed for the supplementary precordial electrode positions listed below:

Second Intercostal Space Level V^2_1, V^2_2, V^2_3, V^2_4, V^2_5
Third Intercostal Space Level V^3_1, V^3_2, V^3_3, V^3_4, V^3_5, V^3_6
Fourth Intercostal Space Level V^4_1, V^4_2, V^4_3, V^4_4, V^4_5, V^4_6
Fifth Intercostal Space Level V^5_1, V^5_2, V^5_3, V^5_4, V^5_5, V^5_6

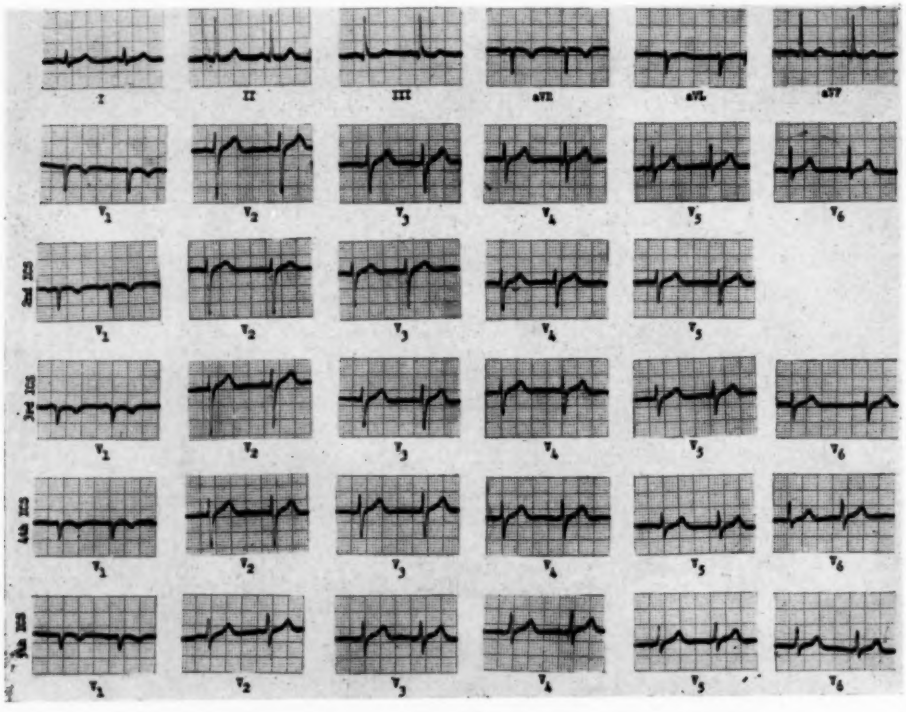

Fig. 1.—Vertical position. Row 1: Regular Leads I, II, III, and routine aV leads. Row 2: Normal V_1 to V_6 leads. Row 3: V^2_1 to V^2_5 leads. Row 4: V^3_1 to V^3_6 leads. Row 5: V^4_1 to V^4_6 leads. Row 6: V^5_1 to V^5_6 leads.

RESULTS

This discussion will merely record observations, most of which can be easily understood from the tables. It was found in the 100 cases of 50 young men and 50 young women that the electrical axis of the heart was 76 per cent vertical, 18 per cent intermediate, and 6 per cent horizontal, the incidence of "electrical positions" being about equal in the two sexes.

The QRS Complex.—Probably the most important aspect of the ECG in the precordial leads is the QRS complex. This project concentrated on the

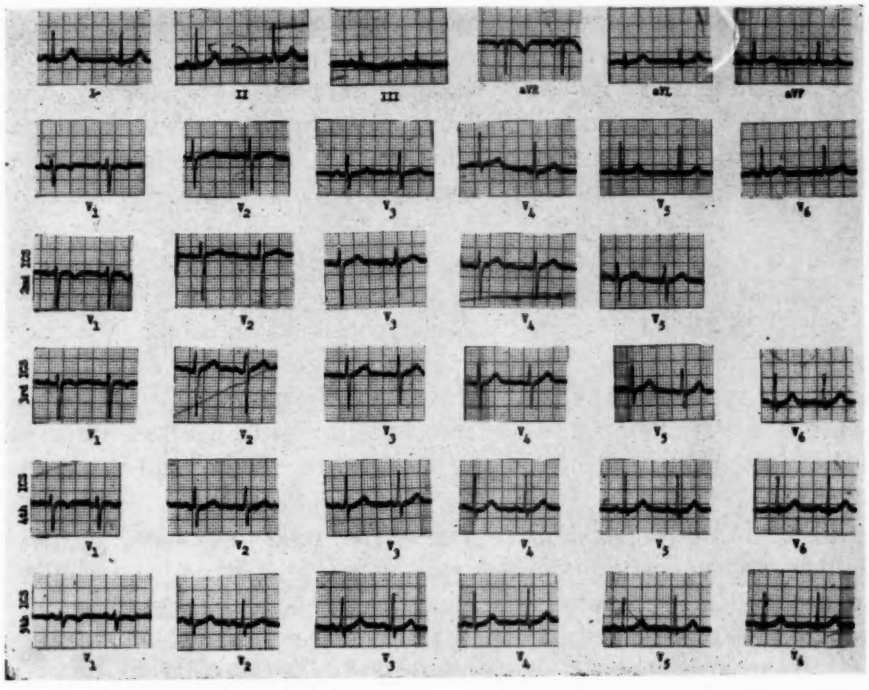

Fig. 2.—Intermediate position. Rows of tracings as in Fig. 1.

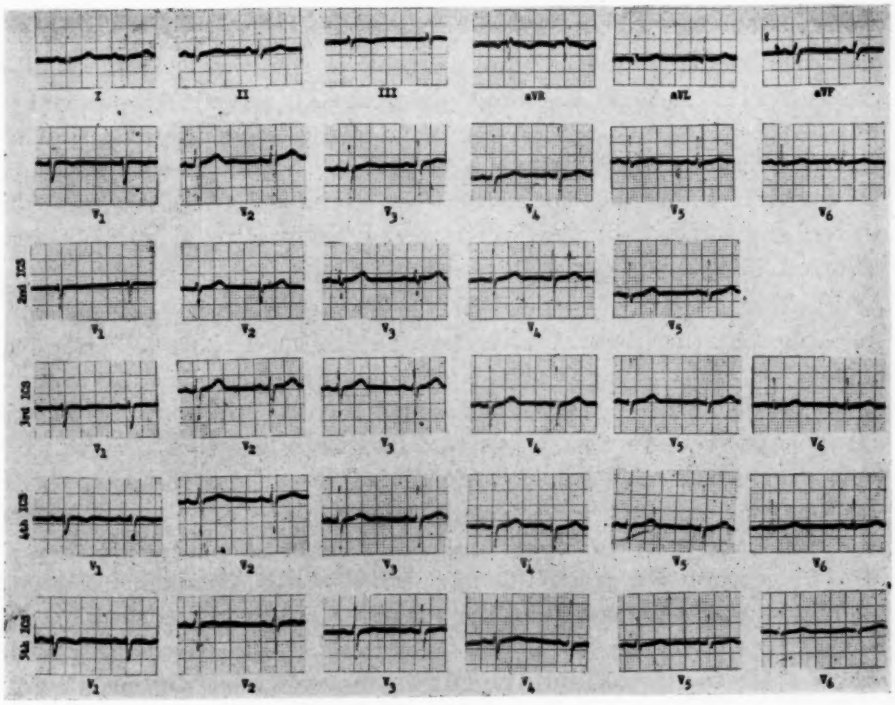

Fig. 3.—Horizontal position. Rows of tracings as in Fig. 1.

pattern of the QRS complex, with special emphasis on the R and S waves (see Table I). In the space V^2_1 the pattern rS sum negative was the most common complex, but the pattern rSr′ sum negative also occurred quite frequently (see Table II). At first is was thought that the rSr complex might be found only in a heart in a vertical electrical axis, but this was not borne out, for it was found in both the intermediate and horizontal hearts. There was also no relation to rotation of the heart.

The initial r deflection in the space, V^2_1, ranged from 0. 0 to 4.0 mm., averaging 1.23 mm. Most commonly, the r wave ranged from 0.5 to 1.5 mm. In five records the QRS complex at this position consisted only of a Q wave. These five records showed the same Q-wave pattern in the V^3_1 and V^4_1 positions. Only two of the five records showed the same Q-wave pattern in V^5_1. There were no Q waves in Lead V_2 in any of the intercostal spaces. All five records showed the heart to be in the vertical electrical axis. None of the records showed any rotation of the heart.

In the second intercostal space, as the electrode was placed further to the left, the r wave became larger, the S wave smaller. The complex usually moved through the stages of rS sum negative, RS sum 0, and Rs sum positive. But even as far out as position V_5, 63 per cent of the records had a QRS complex sum negative. In the position of V^3_4, 71 per cent of the records still had a sum negative complex, whereas in V_5, 52 per cent had a sum positive complex. It was observed that the records showing the most vertical electrical axis became sum positive only in the far left position on the chest. The fourth and fifth intercostal spaces showed much the same pattern, except that the complexes became sum positive in positions further to the right.

The P Wave.—The amplitude and direction of the P wave is indicated quite clearly in Table III. In Lead V^2_1, the P wave was negative in 71 per cent of the cases, but in the next lead, V^2_2, the majority of the waves became diphasic or positive. However, even in V^2_5 there were still seven records with a negative P wave. In the third intercostal space the P wave showed a more definite shift to the positive in Lead V_2. In the fourth and fifth intercostal spaces, only one record showed a negative P wave in position V_2.

The T Wave.—In the V^2_1 position the greater majority (89 per cent) of the records showed a negative T wave (see Table IV). The wave became slowly less negative and more positive as the electrode was moved to the left, and at position V^2_4, 91 per cent were positive, seven records still showing negative T waves. In position V^2_5, there were five records with a negative T wave. In Lead V^3_1, 74 per cent of the records had a negative T wave, and 18 had a positive T wave. At V^3_3, 98 were positive, but as far to the left as position V^3_6 one record had a negative T wave. In the fourth and fifth intercostal spaces all T waves were positive after position V_2, except for one record which remained negative until V^4_4 and V^5_3. It was observed that the majority of the records which showed negative T waves far to the left in the second and third intercostal spaces were in the vertical electrical axis, and the QRS complexes were sum negative to the far left also.

TABLE I. R AND S AMPLITUDES

POSITION	V_1		V_2		V_3		V_4		V_5		V_6	
WAVE	R	S	R	S	R	S	R	S	R	S	R	S
Second Intercostal Space												
Female Range	0.0 3.5	1.5 15.3	0.2 8.0	0.0 17.0	0.0 9.0	0.0 14.5	0.0 7.8	0.0 11.5	0.2 12.8	0.0 10.0	— —	— —
Female Average	1.06	8.65	2.34	9.26	2.53	7.79	2.43	5.37	2.93	4.11	—	—
Male Range	0.0 4.0	0.0 18.0	0.1 9.0	1.0 23.0	0.2 11.0	1.0 20.0	0.5 9.0	2.0 18.0	0.5 8.5	1.0 16.0	— —	— —
Male Average	1.40	9.39	2.67	11.44	2.88	10.08	2.90	7.81	3.14	5.08	—	—
Third Intercostal Space												
Female Range	0.0 4.5	1.4 18.0	0.6 9.0	0.0 23.5	0.3 10.0	0.0 23.0	0.2 12.0	0.4 13.5	0.8 16.4	0.0 11.0	1.0 16.0	0.0 7.0
Female Average	1.74	9.38	3.6	11.14	3.62	8.01	3.81	5.49	4.58	3.72	5.28	2.14
Male Range	0.0 5.5	0.0 22.0	0.3 13.0	4.0 26.0	0.4 12.0	1.0 25.0	0.4 14.0	0.0 18.0	0.4 14.0	0.0 17.0	0.0 14.0	0.0 12.0
Male Average	1.90	10.19	4.17	13.30	4.41	10.82	4.30	7.53	5.91	4.54	7.85	2.12
Fourth Intercostal Space												
Female Range	0.0 6.0	3.0 19.0	0.8 10.5	1.0 27.2	0.5 12.5	0.6 21.5	0.1 13.6	0.0 15.0	2.0 13.5	0.0 10.2	2.5 14.0	0.0 10.1
Female Average	1.88	9.31	4.24	12.08	4.85	8.04	5.89	5.20	7.49	3.24	7.89	1.61
Male Range	0.0 5.0	0.0 0.9	0.4 12.0	4.0 26.0	0.4 18.0	0.0 26.0	0.5 24.0	0.0 18.0	0.5 23.0	0.0 14.0	5.0 19.0	0.0 5.0
Male Average	2.03	9.24	5.14	12.29	7.18	8.57	10.97	5.60	12.04	3.14	11.49	1.19
Fifth Intercostal Space												
Female Range	0.0 18.0	1.5 15.0	0.1 19.0	1.0 20.5	1.0 20.0	0.0 15.0	3.5 17.0	0.0 13.0	3.5 21.5	0.0 8.0	0.0 18.5	0.0 4.0
Female Average	1.87	6.68	5.50	6.83	8.10	4.59	10.28	3.26	10.15	1.80	9.46	0.94
Male Range	0.0 5.0	0.0 20.0	0.5 23.0	0.0 17.0	2.0 25.0	0.0 16.0	4.0 25.0	0.0 11.0	4.0 25.0	0.0 10.0	4.4 23.0	0.0 6.0
Male Average	1.91	6.71	6.50	8.11	11.60	5.92	14.17	3.56	14.50	1.80	12.34	0.76

TABLE II. QRS COMPLEX

	QRS DIRECTION																							
	SECOND INTERCOSTAL SPACE					THIRD INTERCOSTAL SPACE						FOURTH INTERCOSTAL SPACE						FIFTH INTERCOSTAL SPACE					
	V_1	V_2	V_3	V_4	V_5	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6
–Q	5					5						5						3					
rSr′	36	33	24	12	3	11	11	4	1			2						1					
–rS	58	64	68	76	60	83	83	83	70	42	15	91	90	67	42	11	1	89	58	24	6	1	
(0)RS		1	4	2	5		1	4	4	5	12		3	2	4	5	2	2	5	4	3	1	1
(+)Rs			3	9	25		5	8	23	41	32	2	7	29	36	42	32	5	32	60	67	41	25
(+) R				1	2			1		1	4			1		4	8		1	1	1	1	7
(+)qRs					1					9	33			1	15	28	42		3	8	21	44	52
(+)qR					2				1	2	6				2	4	15			2	2	8	13

TABLE III. P WAVE

	SECOND INTERCOSTAL SPACE					THIRD INTERCOSTAL SPACE						FOURTH INTERCOSTAL SPACE						FIFTH INTERCOSTAL SPACE					
	V_1	V_2	V_3	V_4	V_5	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6
P-Wave Amplitude																							
Mean	0.5	0.4	0.3	0.25	0.25	0.4	0.4	0.3	0.3	0.3	0.3	0.4	0.45	0.4	0.4	0.35	3.0	0.4	0.5	0.47	0.42	0.4	0.35
Range	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	1.5	1.0	0.8	1.0	1.0	1.0	2.0	0.8	1.0	1.0	0.8	1.0	1.25	1.25	1.0	1.0	1.0	1.0	1.0	1.0	1.0	0.8	1.0
P-Wave Direction																							
(+)	12	40	43	55	62	44	69	78	83	94	94	79	95	95	97+	99	100	93	98	100	100	100	100
(±)	16	34	19	13	4	40	19	9	6	2	2	17	4	4	0	0	0	5	1	0	0	0	0
(–)	71	22	22	16	7	14	5	7	3	2	1	4	1	1	1	1	0	2	1	0	0	0	0
(0)	1	4	6	16	17	2	6	6	8	2	3	0	0	0	2	0	0	0	0	0	0	0	0

TABLE IV. T WAVE

	SECOND INTERCOSTAL SPACE					THIRD INTERCOSTAL SPACE						FOURTH INTERCOSTAL SPACE						FIFTH INTERCOSTAL SPACE					
	V_1	V_2	V_3	V_4	V_5	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6
T-Wave Amplitude																							
Mean	1.6	1.5	1.7	2.0	2.3	1.25	2.8	2.7	2.8	3.0	2.8	1.25	3.9	4.2	4.2	3.8	3.1	1.0	3.7	4.2	4.1	3.5	3.0
Range	0.2	0.2	0.3	0.2	0.2	0.2	0.5	0.3	0.5	0.3	0.3	0.1	0.4	0.5	0.5	0.5	0.5	0.1	0.2	0.5	0.5	0.2	0.2
	4.5	6.5	6.25	7.0	9.2	3.5	8.0	9.0	8.0	7.0	6.5	6.5	9.5	10.0	10.0	10.0	7.0	4.0	10.0	10.0	10.0	10.0	10.0
T-Wave Direction																							
(+)	8	54	74	91	93	18	86	96	98	99	99	33	97	99	99	100	100	43	95	99	100	100	100
(±)	2	5	6	1	1	17	5	0	0	0	0	7	1	0	0	0	0	6	2	0	0	0	0
(–)	89	39	16	7	5	74	8	4	2	1	1	59	2	1	1	0	0	46	3	1	0	0	0
(0)	1	2	4	1	1	1	1	0	0	0	0	1	0	0	0	0	0	5	0	0	0	0	0

TABLE V. U WAVE

	SECOND INTERCOSTAL SPACE					THIRD INTERCOSTAL SPACE						FOURTH INTERCOSTAL SPACE						FIFTH INTERCOSTAL SPACE					
	V_1	V_2	V_3	V_4	V_5	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6	V_1	V_2	V_3	V_4	V_5	V_6
U-Wave Amplitude																							
Range	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
	0.2	0.4	0.5	0.5	0.5	0.2	0.6	0.5	0.5	0.3	0.6	0.3	0.7	0.75	0.6	0.3	0.3	0.3	0.75	0.3	0.3	0.3	0.2
U-Wave Direction																							
(+)	3	25	33	43	38	6	61	65	67	52	34	11	77	85	73	48	22	13	72	73	50	29	14
(0)	97	75	67	57	62	94	39	35	33	48	66	89	23	15	27	52	78	87	28	27	50	71	86

The S-T Segment.—The S-T segment was somewhat elevated in the precordial leads in the second and third intercostal spaces in a few cases, most commonly in Leads V_1 and V_2. When the elevation was present, it did not exceed 1 mm. In the majority of the records the S-T segment was isoelectric.

The U Wave.—Because of the recent interest[5] in the U wave, it was also studied in the series and is analyzed in Table V. The amplitude of a U wave never exceeded 0.75 mm., and a value this high was found only in the fourth and fifth intercostal spaces, Leads V_2 and V_3. As can be seen from Table V, the U wave is not often present in the second intercostal space, but is more often found in the third, fourth, and fifth intercostal spaces, being most common in Leads V_2, V_3, and V_4. It was interesting to note that in the second and third intercostal spaces the U waves were much more common in men than in women, but that in the fourth and fifth intercostal spaces the occurrence in both sexes was about equal.

COMMENTS

This study has established a norm for the future use of high precordial leads in diagnostic electrocardiography. It demonstrates that an R′ occurred in the leads described in apparently normal subjects. The large amplitude of some of the QRS complexes shows the danger of the use of this parameter alone as an indication of ventricular hypertrophy. A QRS complex demonstrated by a lone Q was present only in leads to the right of the sternum. The absence of single Q's or Qr (sum negative) in the left chest leads in these normal cases should be emphasized. It must be concluded that even in these high leads a single Q or Qr (sum negative) over the left chest is probably indicative of abnormality. The high incidence of negative T waves in leads to the left of the sternum should be remembered in the evaluation of T-wave changes in these areas. The rarity of negative T waves in the fourth intercostal space would make unlikely the assumption that the negativity was a persistence of the juvenile pattern. Finally, it should be observed that there were no negative U waves in this study.

SUMMARY

In order to establish normals for reference in the electrocardiographic exploration of the surface of the chest, a large number of unipolar leads were recorded in 100 normal subjects from sites above the position of the precordial electrode employed in routine electrocardiographic studies, and the records analyzed. Among the observations made are the following:

1. An R′ wave may be recorded in leads from the second and third intercostal spaces, and occasionally in leads to the right of the sternum in the fourth and fifth intercostal spaces.

2. Large amplitude of the QRS complex is not uncommon in high precordial leads.

3. A QRS consisting only of a Q wave, or of a Qr (sum negative), was recorded only in leads to the right of the sternum.

4. Negative T waves were frequently recorded in left precordial position, usually in association with an rS pattern of the QRS complex.

5. S-T segment deviation exceeding 1 mm. was not encountered.

6. U waves, if present, were always upright.

It is planned to employ the multiple leads used in this study in a series of patients with heart disease of various types in order to ascertain whether certain additional leads may yield additional useful information.

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Comparison of Simultaneously Recorded Intra-Arterial and Extra-Arterial Pressure Pulses in Man

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INTRODUCTION

Percutaneous recording of pulses is a well-known method for the study of the properties of arterial walls. Several old, simple methods, such as the optical method used by Frank, have given valuable data in the past,[1-4] but the difficulties incurred in the use of such delicate techniques have prevented their extensive use in detecting contour abnormalities due to normal aging and vascular disease.

The following techniques have been employed recently for such recordings: (a) piezocrystals "properly" applied against the skin,[5-8] (b) photoelectric recording of digital transparency changes,[9-11] (c) electrical resistance recording of a mercury-filled rubber tubing encircling the limb,[12] (d) electrical impedance recording between two skin areas,[13,14] and (e) cuff systems recording the volume oscillations by amplifying the pressure changes of air or water in a rigid case surrounding the limb.[15-19]

Most of these methods have been used in the study of the peripheral vascular bed, and a significant amount of information has resulted from such studies. Vasomotor influences, however, alter the shape of peripheral pulses, and some of these methods have been modified for recording central arterial pulses, which would be less affected by vasomotion.

The experimental procedure has also varied in most cases, especially the pressure with which the pickup device is applied against the skin, thus possibly altering the extra- or intra-arterial pulse contours. In the present investigation we used a cuff system adapted for either central or peripheral arterial pulse recordings under different pressures. Central and peripheral pulses were recorded simultaneously and from the same site intra-arterially and extra-arterially through the cuff, and the effects of altered vascular tone were studied.

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Repeat variability of pulses obtained by using a standardized technique has also been studied, with the hope that consistency of certain pulse items may characterize the individual under study.

METHODS AND MATERIAL

A thin rubber cuff, 3 by 5 cm., with rigid backing is applied against the extremity with varying pressure, and is connected with a 15-cm. long, rigid tubing (PE 280) to a Statham P23AA transducer. The transducer's output is applied to a two-stage push-pull DC amplifier with AC coupling, with time constant of 2 seconds at its output circuit. The natural frequency response of the system in situ is 120 cycles per second, and the response is flat from 0.5 to over 45 cycles per second. The output of the amplifier is fed into the DC section of a two-channel electrocardiograph (Elema, Mingograph 23, frequency response flat to 450 cycles per second) and into an optical galvanometer with a frequency response flat up to 35 cycles per second, reduced to 80 per cent at 45 cycles per second and to 60 per cent at 56 cycles per second. A Waters-Conley camera was used to register optically the obtained pulses, or the Mingograph was used in the studies of repeat variability. The over-all gain of the preamplifier was 800, and the peak-to-peak voltage swing at its output for a typical variation in pressure of 1.0 mm. Hg in the cuff–tubing–strain gauge system was approximately 50 millivolts. The gain was adjusted in each case to get deflections of at least 3 centimeters in height on the 15-centimeter wide photographic paper, or 1 centimeter on the 5-centimeter wide Mingograph paper.

A Cournand needle was inserted into the left brachial artery of 10 of the young men; it was connected with a second P23AA gauge to a strain-gauge amplifier. Simultaneous intra-arterial and extra-arterial pulse contours were obtained with the rubber cuff exactly over the tip of the needle. The mean double-skinfold thickness over the tip of the needle was 2.2 millimeters, and changes in the turgor of the skin by the experimental procedures were not taken into consideration. In the remaining men a 15-gauge needle was inserted into the brachial artery, and a PE90 catheter, 40-45 centimeters long, was advanced up into the arm and into the proximal subclavian artery or aortic arch. External pulses were obtained with the cuff over the low neck so that the upstrokes of the external (carotid) and internal (subclavian) pressure pulses would coincide. Recordings were also obtained from various points along the upper arm, in all cases the cuff being applied exactly over the tip of the polyethylene catheter in the brachial artery. Thus, simultaneous intra- and extra-arterial tracings from several points between the proximal subclavian artery and the mid-brachial artery were obtained in the men under various counterpressures and physiologic conditions. Thickness of the skin of the upper arm and of subcutaneous tissue varied in the subjects; however, external pulse contours from the low carotid artery were similar in contour to intra-arterial pulses from the subclavian artery; this indicates that the tissue between carotid artery and pickup unit, although reducing the portion of the generating force available to the surface, was not distorting it by development of inertial forces.

The response of the two systems in place was compared by cyclic introduction of 0.2 ml. of saline at various frequencies, and was found to be identical, i.e., flat ±5 per cent up to 40 cycles per second. The effects of exercise were studied in 5 subjects on whom tracings were obtained before and as soon as possible after they had walked for 10 minutes at 3.5 miles per hour on a treadmill at a 5 per cent grade. Cold pressor tests were made by dipping the right hand into ice water and taking recordings from the left arm as described above; reflex hypertension was also obtained by voluntary breath-holding for periods of 30 to 60 seconds. The paper speed was constant at 75 millimeters per second, and calibration of the external pulse was obtained by introduction of volumes of 0.2 to 0.5 ml. to approximate deflections of the brachial artery pulse with a cuff pressure of 40 mm. Hg. Because the external pulse size varied markedly with cuff pressure, such a calibration was done only occasionally. Instead, the following relative heights were determined routinely: (1) the ratio of the height at the point of the first anacrotic slowing, a, to the maximal pulse height, b (a/b in per cent); (2) the ratio of the height of the first anacrotic slowing, a, to the height of the dicrotic notch, c (a/c in per cent). In addition, the interval of peak time was determined, i.e., time from onset of pulse to its maximal excursion.

Subjects.—The persons studied were 18 normotensive male "volunteers" in good physical health, who had a mean age of 22.7 years (range: 18 to 32 years). They were catheterized in recumbency after 30 minutes of rest in an air-conditioned room at a temperature of 76°F. Repeat variability of pulses obtained with the cuff from the carotid artery on 2 successive days was studied further on 21 young and middle-aged male mental patients from the Hastings State Hospital. Their mean age was 41.5 years (range: 18 to 65 years).

RESULTS

Effects of Varying Cuff Pressure on Intra-Arterial and Extra-Arterial Pulse.—It has been known for a long time (Marey's principle) that extra-arterial pulses increase in amplitude with increasing counterpressure of the pickup unit up to about diastolic pressure. Sahli[1] reported an "optimal pressure area" around systolic levels; Kettner[16] obtained maximal pulsations at below systolic pressure levels. Fig. 1 shows typical changes in contour of the brachial artery pulse at the elbow as the cuff pressure against the skin is increased from 20 to 140 mm. Hg. It is to be noted that the intra-arterial pressure pulse shows no substantial change, and blood pressure remains at 130/65 mm. Hg throughout this range. The external pulse increases up to 140 mm. Hg and alters its shape as well. At 20 mm. Hg it possesses a short systolic plateau and a very shallow dicrotic dip; grossly, it is a simple triangular figure similar to central arterial pulses. With cuff pressures below 20 mm. Hg the systolic plateau is much clearer, but with increasing pressure the pulse becomes peaked. It is further obvious that the two pulses become identical at levels of 40 mm. Hg, excepting an *undershoot* of the extra-arterial pulse during the rapid rise and fall in the intra-arterial pressure creating the peak; as soon as the cuff pressure reaches the diastolic levels of 60 to 70 mm. Hg, this undershoot disappears, but overshoots appear, becoming more prominent with higher pressures. It should be noted that the middle portions of both pulses (dicrotic notch and rebound) remain relatively unaltered with respect to each other between cuff pressures of 40 and 100 mm. Hg.

The peaking of the systolic plateau of extra-arterial pulses with high counterpressures becomes more obvious in records from more central arteries. Upper brachial, and especially carotid, tracings frequently possess a clear-cut plateau, in both intra- and extra-arterial recordings.[16,20] In such cases, cuff pressures above diastolic pressure distort the central pulse contour, in effect transforming it into a peripheral pulse. Therefore, a subdiastolic pressure of 45 to 60 mm. Hg has been adopted as constant counterpressure in this study.

Fig. 2 shows the change in height of the carotid and the brachial pulses in the same person when the pressure within the recording cuff was increased from 0 to about 200 mm. Hg. The two curves are quite similar, and maximal excursions are obtained with counterpressures between diastolic and systolic levels. In most experiments the maximal pulse heights are obtained with cuff pressures around systolic levels[1]; the intra-arterial pulse is not altered until that level, and only beyond this point are changes consistent with an interrupted blood flow within the artery apparent. It is likely, therefore, that the pressure within the cuff does not reach the walls of the artery under study, and even with greatly suprasystolic pressures resulting in complete occlusion of the artery, impinge-

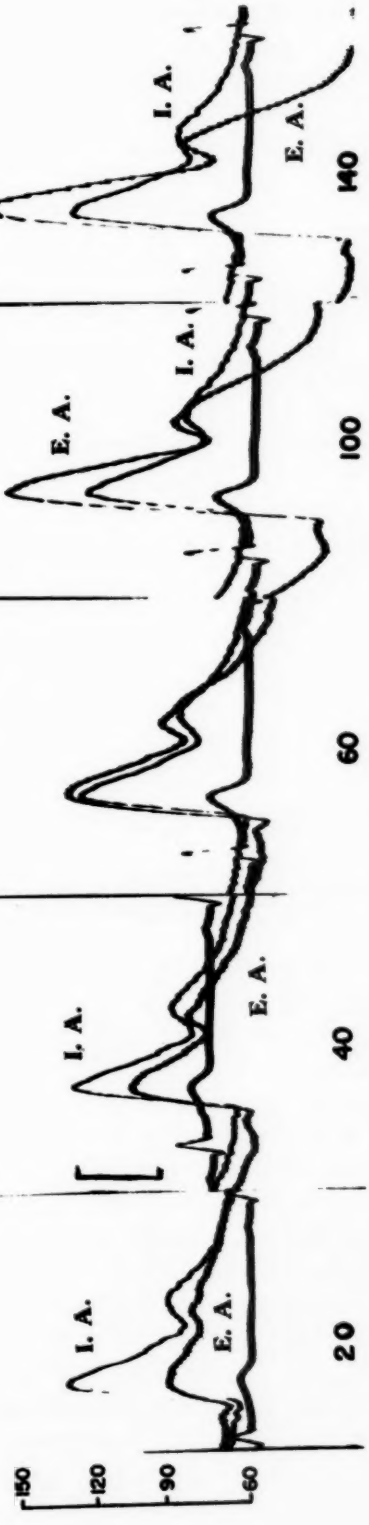

Fig. 1.—Simultaneous intra-arterial (*I. A.*) and extra-arterial (*E. A.*) brachial artery pressure pulses recorded from the same point, with constant gain, but cuff under different pressures; the numbers underneath indicate levels of cuff pressure in mm. Hg. In this and all subsequent figures the pressure levels on the left apply for all intra-arterial pressure pulses. Volume calibration for extra-arterial pulse with 40 mm. Hg pressure = 0.25 ml.

ment of the column of blood against the upper edge of the cuff induces oscillations of the air sufficient to produce a pulse. Thus, the right sections of the curves of Fig. 2 are not symmetrical with respect to the left ones, and if the properties of the strain gauge used would permit application of cuff pressures exceeding 300 mm. Hg, pulsations would be recorded beyond this point.

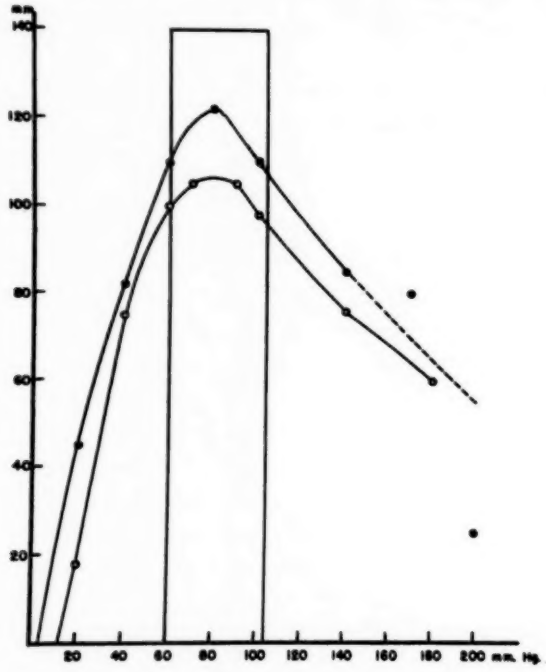

Fig. 2.—Abscissa: pressure within the cuff applied against the skin. Ordinate: transcutaneously recorded pulse height in mm. Upper curve (full circles): left low carotid artery. Lower curve (open circles): brachial artery at elbow. The two vertical lines indicate the intra-arterial pressure at the elbow level (105/60 mm. Hg).

Intra- and Extra-Arterial Pulses During Peripheral Occlusion.—In most of the subjects, circulation in the lower arm was stopped by manual occlusion of the radial and ulnar arteries or by sudden inflation of a cuff on the wrist to levels of 300 mm. Hg; intra- and extra-arterial pulses were obtained from the brachial artery at the level of the elbow. Typical results from such a maneuver, identical to those of Hamilton and Dow[21] are seen in Fig. 3 (see also, Wezler and Böger[4]). In the control, the peak of the extra-arterial pulse obtained with a cuff pressure of 50 mm. Hg is somewhat undershot, but otherwise the two pulses are identical; immediately after the occlusion both pulses become quite "peripheral" in type but their systolic portions are quantitatively different.

Effects of Vasomotion on Intra- and Extra-Arterial Pulse Contours.—Norepinephrine and nitroglycerin were administered to all men; also, the breath-holding and cold-pressor tests were performed in all subjects. Fig. 4 shows the changes in the brachial pulse contour when the blood pressure was moderately raised by infusion of norepinephrine (compare to control records of Fig. 3). The high intra-arterial pressure displays a very marked dicrotic dip, whereas the external pulse shows a reduced amplitude and absence of secondary oscillations.

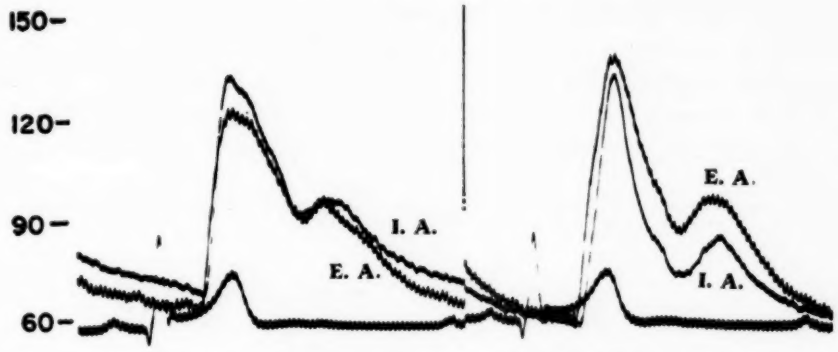

Fig. 3.—Intra-arterial and extra-arterial pulses (at cuff pressure of 50 mm. Hg) of the brachial artery at elbow; the extra-arterial pulses carry a mild 60-cycle interference. *Left:* Control. *Right:* Five seconds after occlusion of circulation to lower arm with a cuff inflated to 300 mm. Hg. Observe the similar qualitative but different quantitative response, the extra-arterial pulse becoming the larger and wider of the two.

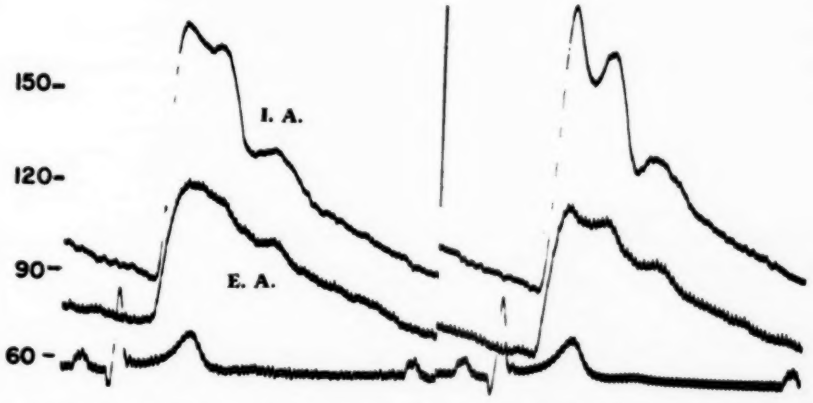

Fig. 4.—As in Fig. 3 (same individual, artery, cuff pressure, and amplifiers' gain), but the tracings were obtained during infusion of norepinephrine. *Right:* After application of 300 mm. Hg of counter-pressure over lower arm.

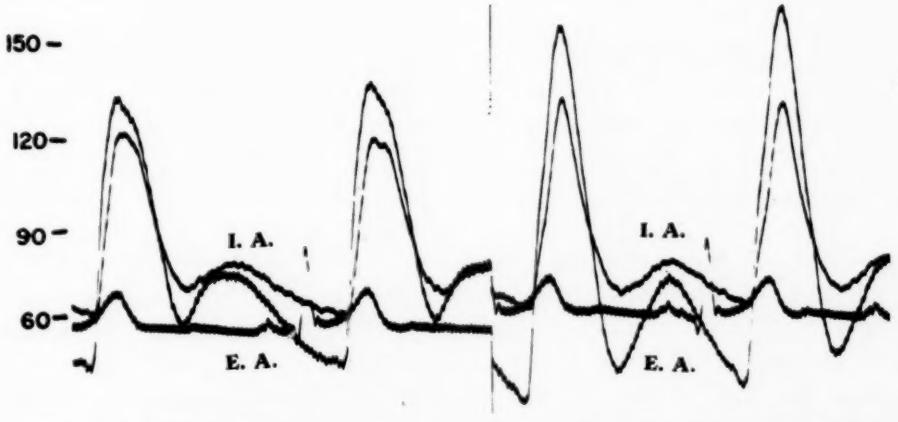

Fig. 5.—As in Figs. 3 and 4, but the tracings were obtained after the administration of nitroglycerin. Intra-arterial pressure is 120/60 mm. Hg before, and 130/60 mm. Hg after, occlusion in the lower arm.

The instantaneous course of the two pulses is at times opposite, the external pulse increasing while intra-arterial pressure may decrease; the anacrotic break in the external pulse, usually more pronounced than here, is not the reflection of any similar change in intra-arterial pressure. This can be described as decreased and "delayed" arterial compliance (see Alexander[22]) after norepinephrine.

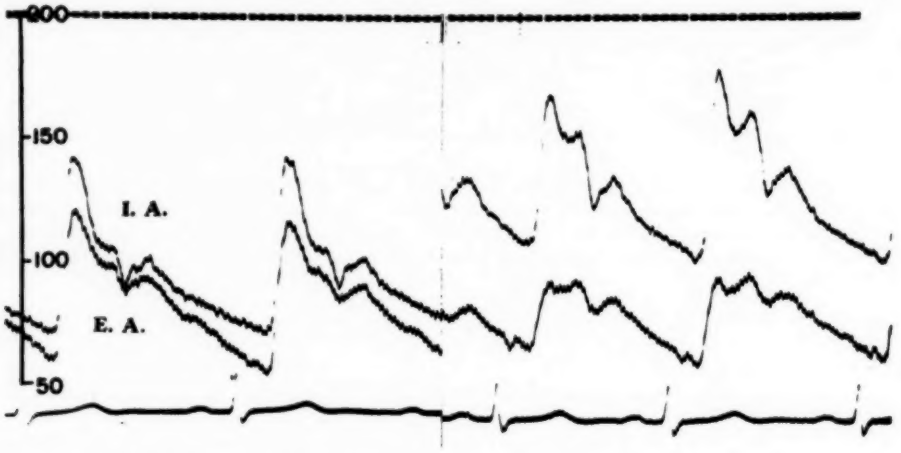

Fig. 6.—*Left:* The curves are intra-arterial (*above*) and extra-arterial (*below*) (cuff pressure of 50 mm. Hg) brachial pulses midway between axilla and elbow. *Right:* The same pulses at 55 seconds of breath-holding. Time above the tracings in 1/25th and 1/5th seconds.

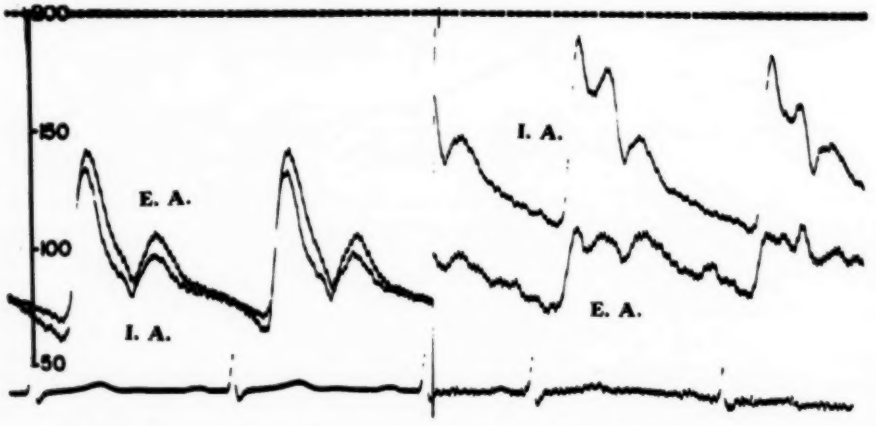

Fig. 7.—As in Fig. 6 (same individual and artery), but after the administration of nitroglycerin to the subject. The resting pulses on the left have different contours than do the corresponding ones of Fig. 6, but at the end of the voluntary apnea they are indistinguishable from them. Muscle tremor in the electrocardiogram.

The opposite changes following sublingual administration of nitroglycerin are shown in Fig. 5. The blood pressure has returned to control levels, but the same external cuff pressure results in oscillations significantly larger than those in the control tracing. With this cuff pressure, therefore, arterial compliance (change in volume per unit of change in pressure) decreases after norepinephrine and increases after nitroglycerin. These changes are further accentuated by peripheral occlusion (Figs. 4 and 5), so that the large intra-arterial reflected waves (of fre-

quency 2 to 8 per second) are extensively damped after norepinephrine, but greatly exaggerated after nitroglycerin in the external pulses. External pulses, therefore, do not reflect passively their generating intra-arterial pressures if the peripheral resistances and the tension of the arterial wall are changed.

Independently of the above-described change in pulse contour, *maximal* deflections obtained from any peripheral artery by using high cuff pressures are essentially identical. Thus, even during the infusion of norepinephrine the (distorted) external pulses will become larger if the counterpressure against the artery is increased significantly, usually well above systolic levels (200 to 300 mm. Hg). Conversely, the large pulses recorded under low cuff pressures with nitroglycerin will not increase much further if cuff pressure is raised above the diastolic. Thus, the maximal possible height of the pulse is the same under normal, dilated, or constricted conditions, and the "decrease" in compliance after norepinephrine is apparent only with cuff pressures giving submaximal pulses; however, "delayed" compliance is quite obvious with any cuff pressure during vasoconstriction, and external pulses are grossly distorted contours of the corresponding changes in intra-arterial pressure.

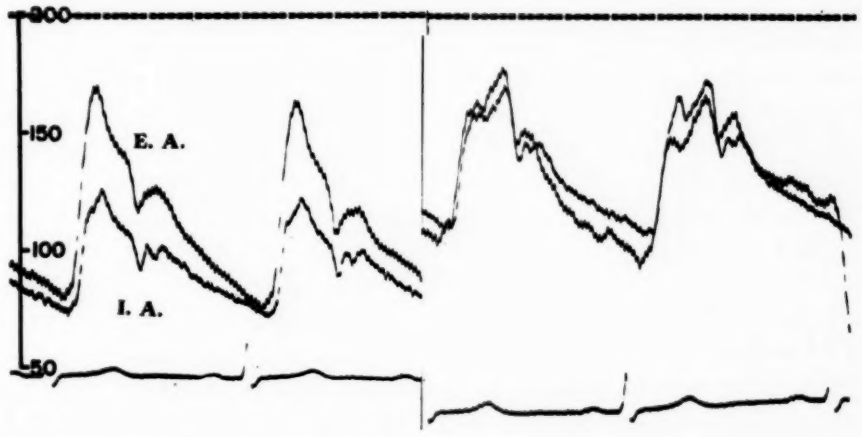

Fig. 8.—Curves from the same subject as in Figs. 6 and 7. The control curves on the left are (*above*) extra-arterial pulse of the carotid artery at 50 mm. Hg cuff pressure, and (*below*) intra-arterial pressure pulse of the proximal subclavian artery. *Right:* Same at the end of a 55-second period of breath-holding (external pulses have slight AC interference). Observe the relatively minor decrease in size of the carotid pulse as compared to that of the upper brachial pulse in Figs. 6 and 7. The swing of the base line at the end of the figure is due to violent inspiration.

Figs. 6, 7, and 8 present changes in pulse contour during acute neurogenic hypertension similar to those during infusion of norepinephrine. The pulses of Figs. 6 and 7 were obtained from the upper left brachial artery between elbow and axilla, before and at the end of 55 seconds of breath-holding. In the control run extra- and intra-arterial pulses are identical; voluntary apnea raises significantly the intra-arterial pressure, whereas the extra-arterial pulse is again decreased and distorted. Administration of nitroglycerin increases the size of the control external pulse (Fig. 7 left, the larger), but does not prevent the hypertension during breath-holding, nor its effects on the external pulse.

These changes are more marked with pulses from peripheral arteries, proportionately more muscular; pulses from *central* arteries are less affected by the same maneuver, despite elevations in blood pressure of equal magnitude. Fig. 8 shows this phenomenon in the same person (extra-arterial pulse is from the low carotid artery, and intra-arterial pulse is from the proximal subclavian artery): the asphyxial rise in blood pressure is the same as in Figs. 6 and 7, but the extra-arterial pulse is only minimally reduced.

To minimize terminal vascular factors in the genesis of these changes in extra-arterial contours during vasoconstriction, the following experiment was done on 4 subjects: the brachial artery in the axilla was compressed between two fingers of an operator, and the intra-arterial pressure in the mid-brachial artery was followed to reach its end point; the artery was then released for one, two, or three pulses into the partially empty arm and then clamped again. This maneuver would also prevent possible interference from altered, longstanding reverberating oscillations of the arterial tree during hypertension. Typical results are seen in Fig. 9. In the control strip the first postrelease extra-arterial pulse is a smaller one with a sharp peak, devoid of plateau, as though the arterial wall were collapsing right after its maximum expansion; the second and third pulses are identical to any of the preocclusion pulses, and none of them shows any anacrotic break despite the undershoot of the plateau relative to the intra-arterial peak (due to the low cuff pressure). During administration of norepinephrine (lower strips) the extra-arterial pulses were mildly abnormal before occlusion, as described above. The first released pulse, however, although *larger* than those before occlusion, is markedly deformed; its anacrotic break occurs well before it reaches its midpoint, during the period of smooth rise in intra-arterial pressure. This break in the upstroke, leading to a late peak, occurs also prominently in the following two pulses. Such abnormalities in contour, therefore, when present in a full or partially empty constricted artery, seem to originate locally rather than from the terminal vascular tree.

Effects of Exercise.—Tracings were obtained immediately before and as soon as possible after the subjects had walked for 10 minutes on the treadmill, as described previously. All 5 subjects showed decreased external pulses following exercise, mainly of the fast deflection. The data are not numerous enough to be evaluated.

Repeat Variability.—The mean of the peak times of the right carotid pulses of the 21 patients, given in Table I, indicated no difference between the two days. The decreased *relative* peak times (peak time over cycle time) on the second day are due to longer cycle times (pulse rate was slower the second day).

The repeat variability is also expressed in terms of variance within individuals (Vwi) as compared with the interindividual variance (Vwd). The day-to-day fluctuations (Vwi) are compared with the interindividual or group variability (Vwd), so as to characterize the accuracy with which the position of an individual within the group can be determined. The reliability is expressed in terms of a coefficient of consistency, $r'c = 1 - \frac{Vwi}{Vwd}$. A value of 0.0 indicates complete

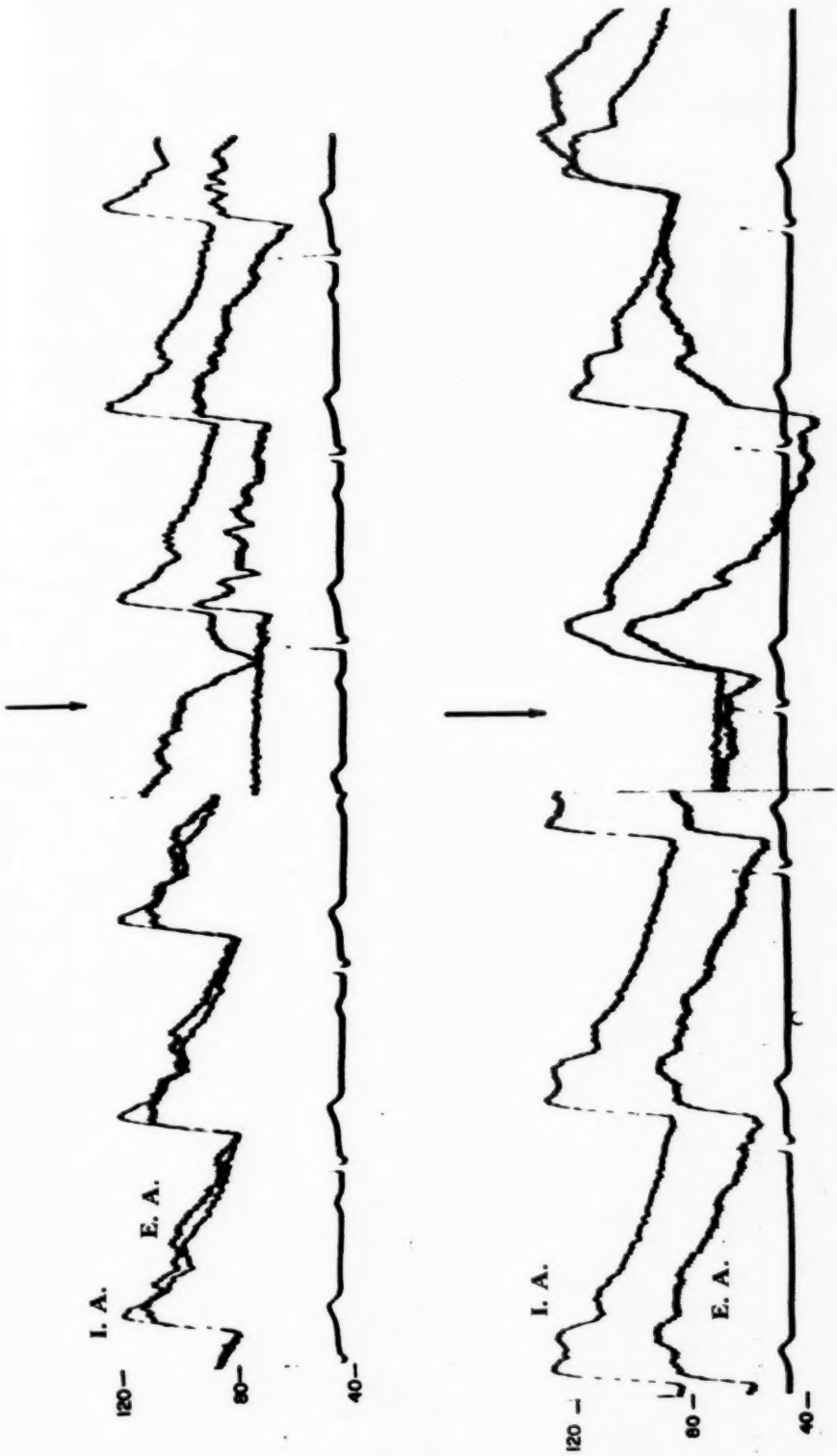

Fig. 9.—*Upper strip left:* Intra-arterial (the peaked pulses) and extra-arterial pressure pulses (cuff pressure 40 mm. Hg) of the brachial artery 10 cm. above the elbow. *Right:* At the arrow the brachial artery, which had been occluded some seconds previously, is suddenly released for three pulses; the upper curves are the intra-arterial. *Lower strip left:* During infusion of norepinephrine. *Right:* Release of the occluded brachial artery. Movement of the base line in the extra-arterial pulse. The third pulses coincide during the upstroke, but the plateau and downstroke of the extra-arterial pulse last considerably longer.

absence of consistency, and a value of 1.0 indicates complete consistency. Arbitrarily, we consider the coefficient of consistency as high for values over 0.8, moderate for values from 0.6 to 0.79, and low for values below 0.6. Table II shows that the variation of the means for each individual about the general mean was significantly larger than the average variation of the two daily values for each individual about their respective means, and that consistency is high for 2 of the 4 values studied.

The ratio of the height at which the first break in the upstroke occurs to the maximal height of the pulse shows the best consistency of all items, and is followed by the absolute peak time. Similar measurements on digital pulses in 26 healthy young men in this same laboratory (Simonson[11]) show a far lower consistency. This indicates that certain items of central pulses are less affected by vasomotor changes than are similar items of purely peripheral pulses; this should not predict the value of either method in comparison between healthy persons and patients.

TABLE I

PULSE WAVE PARAMETER	FIRST DAY		SECOND DAY		Δ (1-2)	
	MEAN	S.D.	MEAN	S.D.	Δ	t*
Peak Time (in sec.)	0.16	0.07	0.16	0.06	0.00	0.06
Relative Peak Time (in per cent of cycle)	19.27	7.05	18.05	6.55	1.22	1.19
a/b (in per cent)	76.08	11.85	77.10	10.27	−1.02	1.15
a/c (in per cent)	142.53	52.36	146.87	59.44	−4.33	0.42

*A value of t greater than 2.09 would indicate a difference significant at the 5 per cent level.

TABLE II

PULSE WAVE PARAMETER	VARIANCE BETWEEN INDIVIDUALS	VARIANCE WITHIN INDIVIDUALS	r′c
Peak Time (in sec.)	0.0078	0.0007	0.83
Relative Peak Time (in per cent of cycle)	81.47	11.31	0.76
a/b (in per cent)	237.54	8.49	0.93
a/c (in per cent)	5159.11	1071.75	0.66

DISCUSSION

Techniques similar to the one described herein have been used for decades in the well-known sphygmographs; this method and most of the recent ones

using highly sensitive elements applied against a small area of skin possess the advantage of simplicity of operation, and through the use of high-gain amplifying systems display contours with features which can be easily analyzed. Increase in the coupling area between skin and sensing element would result in decreased differentiation of recorded pulses.

The present method cannot be used for registration of blood pressure; the junction between skin and sensing element should be a liquid one in a rigid case, and the amplifier should have no capacitors in its exit. However, pulse contours obtained herewith may indicate certain arterial properties not obtainable by arterial catheterization.

The recorded extra-arterial pulse contours closely resemble intra-arterial ones only at recording cuff pressures slightly below diastolic levels. Disfiguration of the pulse by high cuff pressures is not important if peripheral pulses are studied, because it tends to accentuate their normal double triangular configuration. However, central intra-arterial pressure pulses are significantly different from peripheral ones,[20,23] and supradiastolic counterpressures will create peaks on the plateau of external central pulses, simulating anacrotic breaks; on the other hand, very low counterpressures will result in pulses selectively undershot during rapid phases. Thus, counterpressures of 45 to 60 mm. Hg have been adopted routinely, and central pulses thus recorded are constant per individual, with insignificant day-to-day variations. Under these conditions an extra-arterial and an intra-arterial pulse contour from two different central arteries may be quite alike (Fig. 8, right); this indicates that the effect of inert structures between arterial wall and recording cuff is relatively constant and, with the employed technique, may be disregarded.

Vasoconstriction reduces markedly the extra-arterial brachial pulse, but only mildly the carotid pulse size, thus limiting the usefulness of the brachial pulse as a constant item of the individual under study. This decreased size of the pulse may be due to one of many causes: a reduced compliance of the arterial wall, a lower effective cuff pressure, or a decreased radial expansion of vessels in hypertension, independent of changes in compliance.

A true reduced compliance or a nonlinear pressure-volume relation is suggested by the selective damping of intra-arterial pressure waves of a frequency of 5 to 10 per second occurring at *below maximal* levels of pressure (Fig. 4, right). This has been known for decades from data on excised vessels (e.g., Wezler and Böger's review article[4]). Secondly, vasoconstriction flattens and shifts the pressure-expansion curve to the right (Fig. 2); thus, the same cuff pressure results in smaller deflections, because the "operating point" is, in effect, transposed to the left. Finally, nonlinear pressure-volume curves could be the result of increased arterial diameter in hypertension; with larger diameters, equal change in volume will be obtained by smaller radial expansion (volume being a reflection of the square of the radius). The relative importance of the first two possibilities is difficult to assess with the present data. If the last possibility were a significant factor, changes in pulse ought not to be observable with minimal changes in blood pressure and in partly empty arterial trunks. Fig. 9 (lower right, external

pulses) indicates that the *size* of the external pulse is indeed restored to above normal by partial arterial emptying, but the *contours* of the pulse remain distorted after this maneuver. Thus, the last possibility seems confirmed here, and dimensional changes of external pulses can be dissociated from temporal changes in the same pulses. The increased size of the first postrelease pulses may be due to a water-hammer effect.[24] However, the external pulses remain larger even on the third beat, whereas intra-arterial pressure pulses are back to normal; again this indicates that the response of the arterial wall is independent of the generating intraluminal pressures.

In vasodilatation the same factors operating in reverse may be responsible for the increased height of the pulse with subdiastolic cuff pressures. Different vasomotor tones seem to be the reason for the reported varied optimal pressures of pickup elements.[1,3]

Delayed arterial compliance in vasoconstriction is obvious with any counterpressure, in full or partly empty arteries. Vasoconstriction therefore generates inertial components, besides exerting purely dimensional effects on the expansion of arterial walls. Delayed compliances have been reported by Alexander and associates[22] in the dog's portal bed with rates of inflow up to 1 ml. per second. In segments of the thoracic aorta of dogs, the same author,[25] by using inflows of 10 and 100 ml. per minute, found a significantly greater distensibility in the constricted state, due to the fact that the constricted aortas had in the empty state half of the initial volumes of the dilated ones. This apparent discrepancy with our findings is due to the fact that our observations were made on full arteries and at rates of inflow many times higher.

Wiggers and Wégria[26] also observed a diminution in excursions of the thoracic aorta of dogs during the early phases of reflex or epinephrine hypertension. In none of their figures was the relative size of the pulse (obtained without counterpressure) decreased by more than 50 per cent during hypertension, as was usually observed in the human brachial artery herein; in our experience, the human carotid artery responds to acute hypertension much as does the canine aorta. Rushmer,[27] using a mercury-filled tubing stretched around the aortic arch of dogs in situ, found a more rapid expansion of circumference than proportionate rise in pressure in early systole. Both acetylcholine and vagal stimulation diminished the circumference excursions but increased the pressure excursions, and thus resemble in action the norepinephrine used in our cases. Rushmer attributes his results, which differ from those of Wiggers and Wégria, to the proximity of the left ventricle, which by pulling lengthwise imparts energy to the aorta during systole; the initial high tension of the sensing element around the arch, which is decreased with hypotension, may also be a contributing factor.

Isotonic measurement of changes in volume or circumference is not easily obtained in systems in which air pressure is applied against a transducer; the participation of changes in volume will be smaller if the volume of air is reduced or replaced with water. The proper term for tracings obtained with air-filled systems under pressure should be "pressure plethysmograms" (Sahli[1]).

Local loss of elasticity can be expected to alter the contour of recorded pulses just as does increased peripheral resistance, i.e., by prolongation of the

systolic duration and appearance of anacrotic breaks; there, methods like the present one may be helpful in following either "degenerative" changes or changes secondary to arterial hypertension; in aortic coarctation, in which both factors are present, these features are quite prominent in the carotid and even in the brachial pulses (Duchosal et al.,[28] 1956; Karpman, 1958). Normal aging may be associated with similar qualitative changes in arterial properties, and studies on older persons have shown upstroke abnormalities and increased "crest" times in central and peripheral pulses[8,11] similar to those artificially induced in young normotensive men in the present study.

SUMMARY

Oscillations of large superficial arteries (brachial and carotid) have been obtained by application of a small cuff with varying pressure, connected to a pressure transducer and amplifier, and recorded by means of optical galvanometers or through a high-frequency, direct-writing (jet) recorder. Simultaneous intra-arterial pressure pulses were obtained from the same arteries by conventional means.

Extra-arterial pulses from young males resemble intra-arterial pulse contours if the cuff pressure is kept at slightly infradiastolic levels. Cuff pressures below as well as above diastolic level yield, respectively, smaller and larger pulses, but the contours of these pulses are distorted as compared to intra-arterial pressure curves. Intra-arterial pulse contours are unaffected up to cuff pressures approaching systolic levels.

In humoral or reflex hypertension, extra-arterial pulses obtained with infradiastolic cuff pressures show decreased height, anacrotic breaks, and a late peak; these changes occur less prominently in the carotid than in the brachial artery, and can be interpreted as indicating that under submaximal cuff pressures the brachial artery displays a decreased and delayed compliance to changes in intra-arterial pressure. Maximal, but nevertheless distorted, pulses will be recorded if cuff pressure is increased to suprasystolic levels. In vasodilatation, maximal pulses are obtained with infradiastolic cuff pressures. Arterial occlusions induce acute, similar increases in the size of intra- and extra-arterial pulses.

An approximate estimate of the degree of central arterial distensibility was suggested by determining in carotid pulses (cuff pressure at 50 mm. Hg) the ratio of the height at the point of the first anacrotic slowing to the total pulse height in per cent. This was found to be constant from day to day in 21 middle-aged patients; the peak time and relative peak time were also found to be consistent between days in the same individuals. A study of these features of the carotid pulse in three major age groups has therefore been completed and the results will be reported separately.

The author is indebted to Dr. Ancel Keys and Dr. Ernst Simonson for much helpful criticism, and to Dr. S. W. Hoobler, of the University of Michigan, for his encouragement and suggestions, which led to the present work. Mr. Walter Carlson gave invaluable assistance during the catheterizations.

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Case Reports

Lipoma of Heart

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Previous cases of primary cardiac tumors have been exceedingly rare. Albers,[1] in 1856, first reported a case of primary lipoma of the heart. Subsequently, there have been several articles adequately surveying the literature in regard to the occurrence and classification of primary cardiac tumors. The reports of Martin,[2] in 1929, and Mahaim,[3] in 1945, included not more than 35 primary cardiac lipomas from the literature and accounted for less than 10 per cent of primary cardiac tumors. Since 1945, three isolated cases of primary cardiac lipomas have been reported.[4-6] Theories as to the etiology have been adequately discussed by Petrucchi,[7] Thorel,[8] Saphir and Corrigan,[9] and Gould.[6]

CASE REPORT

M. H., a 64-year-old woman, was first admitted to the hospital on Jan. 12, 1957, because of a 35-year history of buzzing in the right ear, and a 3 to 4-year history of drooping of the right side of the mouth and inability to close the right eye. These findings had been associated with increasingly frequent right-sided headaches. There was no associated nausea or vomiting. Past history and review of systems were noncontributory.

On physical examination, the temperature was 98° F. The blood pressure was 150/80 mm. Hg. The pupils were round, regular, and reacted equally the same to light and accommodation. Horizontal nystagmus was present. There was no papilledema. Peripheral reflexes were physiologic, and sensory perception was intact. A right-sided weakness of cranial nerves VII and VIII was present.

Hematologic and urinalysis values were within normal range. Spinal fluid examination revealed 77 mg. per cent protein and 1 lymphocyte per high-power field. The electrocardiogram revealed a normal rhythm and conduction except for ventricular premature beats from different foci, demonstrable in Lead I.

On Jan. 15, 1957, a right cerebellar pontine-angle tumor (auditory neurinoma) was removed. At surgery, respirations ceased for a 15-minute interval, during which time respirations were maintained by positive pressure procedure. Auricular fibrillation followed this episode, and 24 hours after surgery the patient expired.

Postmortem examination revealed postoperative intracranial bleeding. On examination of the heart, a tumor measuring 2.5 by 1 by 0.6 cm. was located between the left ventricular medial

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Fig. 1.—Gross specimen of heart looking into left ventricle, demonstrating projecting lipoma.

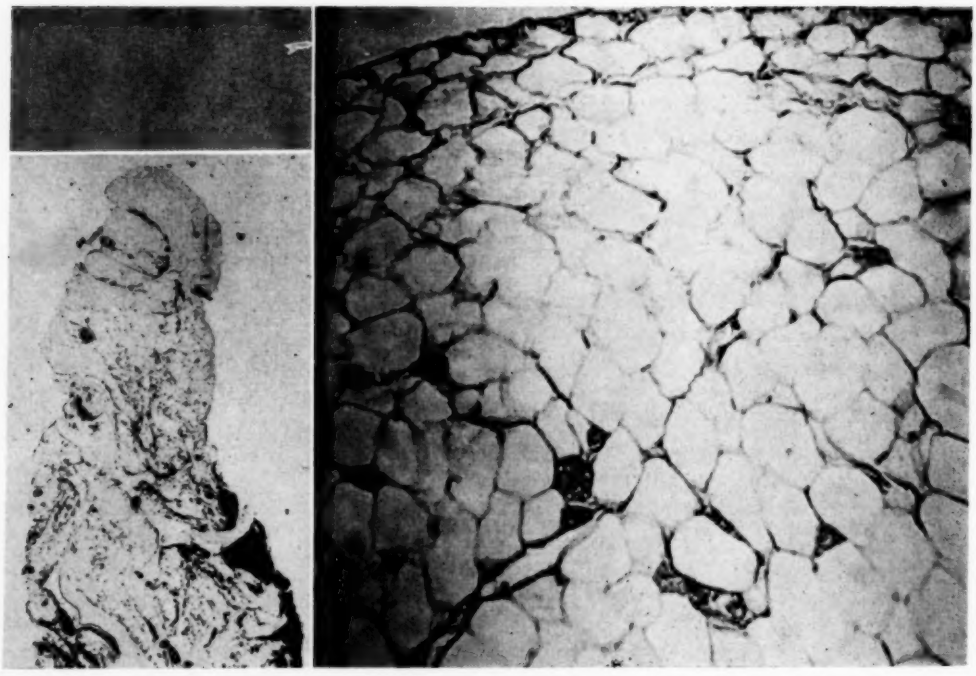

Fig. 2.—*Left*: Microscopic section of lipoma. *Right*: Section showing mature adipose cells and interspersed myocardial cells. Surface covered by endocardium.

papillary muscle and the interventricular septum. The tumor was bright yellow in color, with a glistening, slightly lobular external surface. Sectioning revealed a greasy homogeneous tumor, the broad base of which merged irregularly with the major portion of the subjacent myocardial wall. The heart weighed 260 grams, with slight left ventricular hypertrophy, the left ventricular wall measuring 1.3 cm. in thickness at the base.

Microscopic examination of the cardiac tumor revealed a polypoid structure composed primarily of mature fat cells. The projecting surface was covered by endocardium. The attached base of the tumor irregularly involved the myocardium and revealed aggregates of mature adipose tissue with interspersed myocardial fiber groups. The adipose tissue was not demonstrated to be associated with the epicardium.

The principal final pathologic diagnoses were primary subendocardial polypoid simple lipoma of heart, slight postoperative posterior fossa intracranial bleeding, arteriosclerotic heart disease, moderate acute pulmonary hyperemia, and arterial nephrosclerosis.

COMMENT

The cardiac lipoma was clinically asymptomatic and unsuspected. Most reported cases, except those involving valvular areas by direct attachment or pedunculation or occupying a large portion of the pericardial cavity, have been asymptomatic and, apparently, clinically unimportant. It is conceivable that interference with cardiac conduction may occur. We do not necessarily infer this effect in this case. The combination of an auditory neurinoma and cardiac lipoma has been suggested as a manifestation of tuberous sclerosis. Other associated lesions of this entity were lacking, however.

CONCLUSION

A report of primary lipoma of the heart has been added to the literature.

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1:1 Atrial Flutter With the Wenckebach Phenomenon

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Atrial flutter is almost always associated with atrioventricular block of varying degree. A ventricular response of 1:1 is indeed rare and constitutes a serious cardiac emergency. A review of the literature uncovered less than 50 authenticated cases[6,11] in which the ventricle responded to every atrial impulse. The block of atrial flutter is most commonly of the Type II of second-degree atrioventricular block, and is characterized by P-R (F-R) intervals that remain constant, with one or more P (F) waves that are not followed by a ventricular response. The Wenckebach phenomenon, or Type I of second-degree block, is seldom seen in atrial flutter as the sole manifestation of an atrioventricular conduction disturbance. A recent case report by Brotmacher[3] referred to only two previous instances of this phenomenon. Katz and Pick[9] show two figures (Figs. 231 and 251) of this arrhythmia in their recent book.

This report illustrates another instance of the Wenckebach phenomenon in a patient with atrial flutter and clinical manifestations of hyperthyroidism.

CASE REPORT

The patient a 48-year-old Negro woman, was seen initially in November, 1958, for symptomatic obesity. She was next seen on April 23, 1959, in the Gastrointestinal Clinic, complaining of backache, sour stomach, anorexia, nausea, and a dull, indefinite abdominal pain not influenced by posture, food, or bowel movement. She had normal bowel function and no dysphagia, vomiting, borborygmi, melena, or change in the color of skin, urine, or feces. Within the preceding month she had noted a loss of 18 pounds to a weight of 180 pounds.

Examination revealed an obese woman with a firm nodule in the right lobe of the thyroid, a heart rate of 90 per minute, blood pressure of 125/70 mm. Hg, a Grade 2 systolic murmur, and a soft liver edge just palpable on deep inspiration. The remainder of the examination was normal.

Routine laboratory studies, including complete blood count, fasting blood sugar, blood urea nitrogen, and Bromsulphalein retention, were normal. Ancillary studies, including sigmoidoscopy, x-rays of the stomach, duodenum and colon, and gastric analysis, were normal. The oral cholecystography revealed faint concentration of the contrast material in the gall bladder and numerous multifaceted calculi. Chest x-ray showed the cardiac silhouette to be top normal in size.

On June 1, 1959, she was referred for evaluation to the cardiac clinic, where she complained of exertional dyspnea. Examination revealed her weight to be 155 pounds, pulse 80 per minute, respirations 28 per minute, and blood pressure 130/70 mm. Hg. There was a slight tremor of the

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hands, a bilaterally enlarged thyroid, no abnormal eye signs, a warm moist skin, and a Grade 2 precordial systolic murmur. The basal metabolic rate was +35. On her return visit she complained of some malaise and weakness, and was started on methimazole, 10 mg. four times daily, and phenobarbital, 32 mg. three times daily.

She came to the Accident Ward on June 29, 1959, complaining of nausea and vomiting during the previous 4 days. The vomitus was dark green in color and bitter. She stated that she felt generally sick and short of breath.

Examination revealed an apprehensive and extremely agitated Negro woman appearing chronically ill. Her weight was 136 pounds, a loss of 62 pounds since the beginning of her illness,

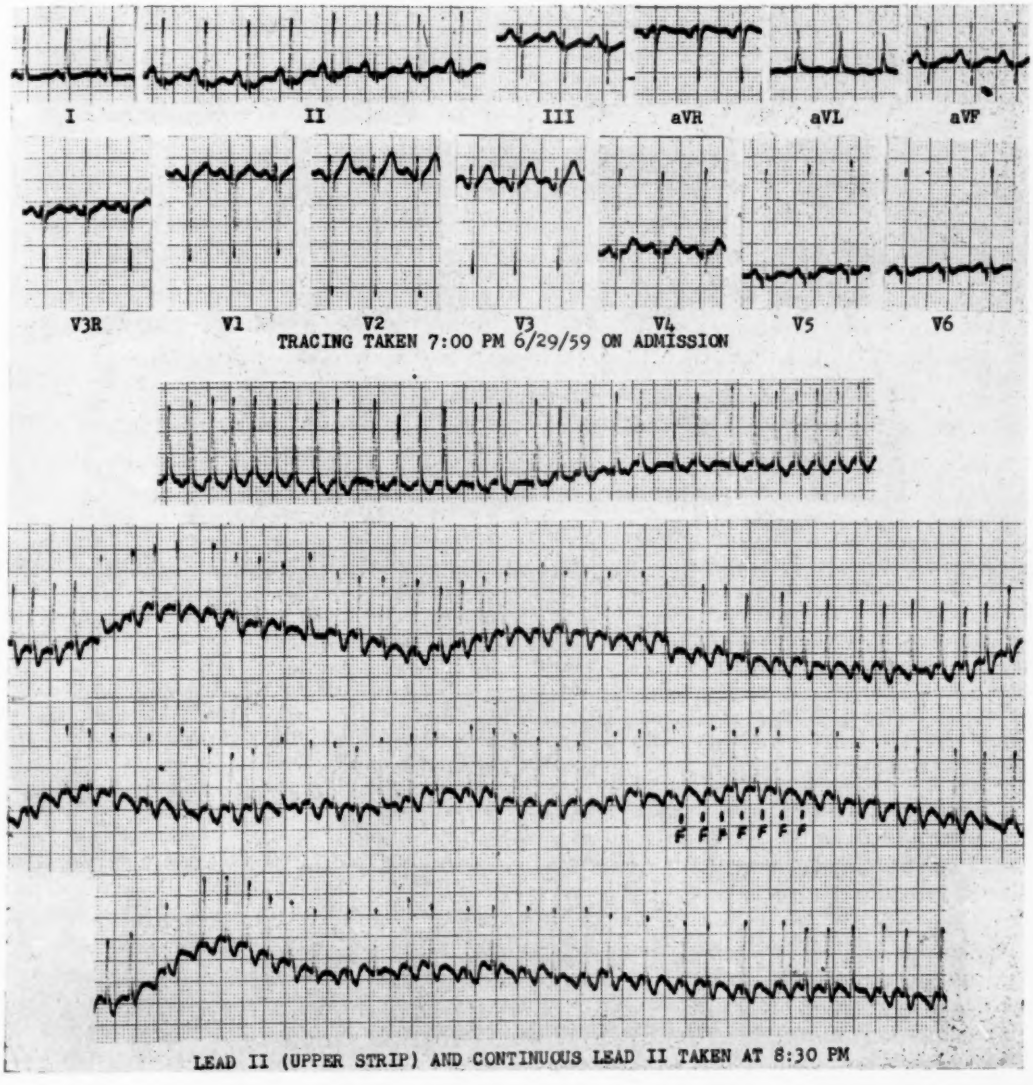

Fig. 1.—The upper tracing denotes a sinus tachycardia with a rate of 150/min. The lower tracing reveals periods of 1:1 atrial flutter at a rate of 300/min. and an area demonstrating the Wenckebach phenomenon. There are occasional nodal extrasystoles. The atrial mechanism is undoubtedly flutter and is better appreciated in, and identical to the F waves seen in, the upper tracing of Fig. 2, where the A-V block is increased. Note during the Wenckebach periods the progressive lengthening of the F-R intervals, the dropped beat, and the longer R-R interval at the beginning as compared to the last R-R cycle length.

height 67½ inches, pulse 150 per minute, respirations 32 per minute, and blood pressure 120/80 mm. Hg. There was a marked tremor of the outstretched hands, and a staring visage, but no other abnormal eye signs. There was a diffuse nontender enlargement of the thyroid gland to about three times normal size, with an audible bruit. The lungs were normal to percussion and auscultation. The heart was enlarged almost to the anterior axillary line on the left, and a Grade 3 precordial systolic murmur was noted. The abdomen was soft, with no palpable organs, masses, or tenderness. The deep tendon reflexes were normal.

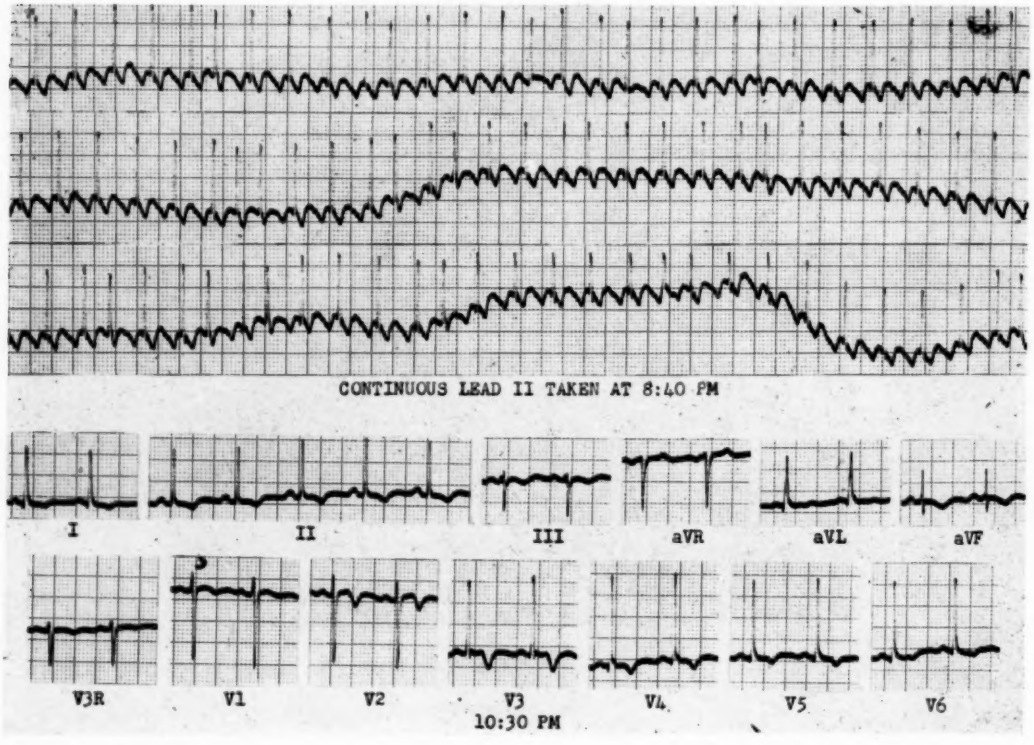

Fig. 2.—The upper electrocardiogram demonstrates that the atrial flutter has changed to a 2:1 atrioventricular block, with occasional ventricular beats responding to every atrial beat. The F waves show the typical saw-tooth configuration of flutter and do not extend along the isoelectric line. The lower tracing reveals normal sinus rhythm with a ventricular rate of 100/min.

She was admitted to the hospital with a tentative diagnosis of thyroid storm. Because of her agitation she was given 100 mg. of sodium phenobarbital intramuscularly at 6:45 P.M., just prior to admission. On admission she was placed in an oxygen tent, and 1.25 mg. of reserpine was given intramuscularly. An initial electrocardiogram taken at this time (Fig. 1) shows a sinus tachycardia with a rate of 150 per minute. She became increasingly dyspneic, and her blood pressure fell to 100/70 mm. Hg. She was seen at frequent intervals, and it was noted at 8:25 P.M. that she developed so rapid a pulse rate that it could not be counted. The patient did not appear to deteriorate with the more rapid heart rate. An electrocardiogram taken at 8:30 P.M. showed initially a 1:1 response with a rate of 300 per minute, which slowed to 240 per minute with the appearance of the Wenckebach phenomenon. An intravenous infusion of hydrocortisone, 100 mg. per 1,000 c.c. of 5 per cent glucose in water, was begun at 8:30 P.M., and 0.8 mg. of lanatoside C was injected through the rubber tubing at 8:40 P.M. An electrocardiogram taken just before had revealed a 2:1 atrial flutter with occasional 1:1 response (Fig. 2). At 9:00 P.M., 1.25 mg. of reserpine intramuscularly was repeated. An electrocardiogram taken at 10:30 P.M. revealed a normal sinus mechanism at a rate of 102 per minute (Fig. 2). Digoxin, 0.25 mg., was given at 10:45 P.M. The intravenous hydrocortisone was continued, and she had no recurrence of the flutter. Oxygen therapy was discontinued the next morning.

Laboratory studies the next day, including complete blood count, fasting blood sugar, blood urea nitrogen, electrolytes, and urinalysis, were normal, except for a serum cholesterol of 90 mg. per cent.

She was stabilized on a therapeutic program of digoxin, 0.5 mg. daily, methimazole, 10 mg. four times daily, cortisone acetate, 25 mg. every 8 hours, sodium phenobarbital, 100 mg. every 6 hours, Lugol's solution, 0.6 c.c. every 6 hours, and aqueous penicillin, 500,000 units every 6 hours. The cortisone acetate was withdrawn slowly over the next 2 weeks. The digoxin was decreased to 0.25 mg. daily, and the penicillin was stopped after 4 days.

Re-evaluation on July 22, 1959, revealed a basal metabolic rate of +14 and a serum cholesterol of 215 mg. per cent. She had gained 6 pounds to 142 pounds, experienced no apprehension for the first time in months, and had lost the tremor of the hands and other signs noted on admission. There had been no subsequent arrhythmias.

DISCUSSION

This 48-year-old woman was seen initially with postural symptoms due to obesity. She lost 62 pounds over a period of 3 months, without dietary effort. In addition, she manifested dyspnea, weakness, warm moist skin, tremor of the hands, staring visage, an enlarged thyroid with a bruit, tachycardia, basal metabolic rate of +35, and a decrease in serum cholesterol to 90 mg. per cent. The clinical diagnosis of hyperthyroidism is definite, although iodine studies were prevented by the recent cholecystography.

Fig. 1, recorded shortly after her admission, illustrates a rapid ventricular rate of 300 per minute, decreasing to 240 per minute with the appearance of the Wenckebach phenomenon, without aberration of the ventricular complexes. Absence of QRS aberration at this rapid rate suggests that there is relatively little disease of myocardial muscle or of the His system. The deflections which suggest atrial flutter in Fig. 1 may be better appreciated after the development of a 2:1 block with occasional conducted 1:1 beats in Fig. 2.

It may be seen in Fig. 1 that the downward slope of the P (F) waves vary in their relation to the succeeding QRS complexes and demonstrate the prolongation of the P-R (F-R) interval characteristic of the Wenckebach phenomenon. The QRS spacing also illustrates the progressive shortening of the R-R interval from the first two complexes to the last two complexes between dropped beats. Not all of the tracing demonstrates this type of conduction, since a 1:1 response occurs at several places, interrupting areas of manifest Wenckebach phenomenon or Type-I block. At no time was atrial fibrillation recorded in the conversion of the flutter to normal sinus rhythm.

Several cases of this phenomenon have been reported. Brotmacher's case[3] demonstrates an atrial rate of 260 per minute in a 53-year-old man with an irregular ventricular rate in a trigeminal grouping. The F-F intervals are not isoelectric. Wenckebach periods are clearly seen. One of the references quoted by Brotmacher, the illustration in Scherf and Schott's book,[13] demonstrates an atrial rate of 215 per minute with isoelectric P-P intervals and probably falls within the classification of atrial tachycardia with block. The authors do not call this an illustration of flutter, but only of paroxysmal supraventricular tachycardia. The illustration of Lewis,[10] also referred to by Brotmacher, demonstrates in a child an atrial rate of 290 per minute, with some QRS aberrations and the

Wenckebach phenomenon as the sole observable A-V conduction defect. The illustrations given by Katz and Pick[9] are clearly instances of flutter demonstrating area of block of only the Wenckebach type. Other reports alluding to the Wenckebach periods in flutter,[2,7] including that of Cloetens and Brandes,[5] demonstrate this block superimposed upon a basic 2:1 A-V block. There are, then, 4 cases previously reported of this phenomenon in a basic 1:1 atrial flutter.

It has been stated that in the presence of a primary 2:1 block the Wenckebach periods may be seen in 50 per cent of the cases of atrial flutter.[2] These instances have been adduced to support the argument that two levels of block exist in the atrioventricular node. The higher level is presumed to be at the junction of the atrial muscle and nodal tissue and to represent the inherent refractoriness of the node to stimulation beyond a critical rate. In this case there was no evident refractoriness of the node to the atrial impulse, as demonstrated by the 1:1 conduction response. The lower level of block, assumed to be responsible for the Wenckebach response, was apparently the only level at which obstruction occurred initially in this patient. With the subsequent tracing, Fig. 2, a 2:1 block has occurred. It is not apparent whether this represents block at the higher level, or whether this represents a gradual extension of the block from the lower level.

The influence of drugs upon this phenomenon is not clear. The digitalis was not administered until after there had been conversion to essentially a 2:1 block. The previous drugs included phenobarbital, given because of the extreme apprehension and agitation in the Accident Ward, and reserpine. The reserpine was administered on the basis of the reports[1,4] suggesting its value in the therapy of thyrotoxicosis. It is also well known that reserpine has a bradycardic effect which may be abolished by atropine, and which is not observed in the heart-lung preparation.[12] This evident vagal effect of reserpine may have tended to increase the degree of atrioventricular block in what otherwise might have been a persistent 1:1 conduction in atrial flutter. The reserpine was not continued in this patient, and she responded to more accepted measures.

SUMMARY

A case is presented demonstrating the presence of 1:1 flutter developing primarily the Wenckebach type of atrioventricular conduction defect.

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Review

Some Considerations Regarding Obscure Diseases Affecting the Mural Endocardium

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INTRODUCTION

This review has been written at the invitation of the Editor and presents the personal views of one pathologist on certain obscure diseases affecting the mural endocardium of the heart chambers and resulting in endocardial thickening. It makes no claim to be a comprehensive review, for the center of the African continent is no place in which to write a comprehensive review, and many excellent papers, particularly from the continent of Europe, have not been consulted. It could not have been written at all were it not for the generosity of cardiologists and pathologists in many countries who have made specimens, photographs, papers, and information available to the writer.

It is then written from a highly personal viewpoint, and I have attempted to make my own views as clear as possible, well realizing that they may be unacceptable to others and that there is ample room for dispute. No special authority other than interest is claimed. Moreover, the results of the study of one particular local disease are stressed so that this disease may be compared with disease conditions of the heart elsewhere, for there seems to be much need of this. Considerable confusion surrounds certain of the conditions which will be discussed. In part, this is inherent in the obscurities of the states themselves, in part to their comparative infrequency or geographical distribution, in part to semantic muddling, and in part to inadequate description, perhaps aggravated by editorial reluctance to grant adequate space to descriptive matter, but in part also to fear and timidity.

The world of medicine is made up of the "lumpers" and the "splitters": those who "lump" conditions together, as an aid to description and memorizing

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and particularly in teaching, or sometimes out of an inborn conservatism of mind, and those who "split" conditions into numerous entities. The "lumpers" are usually in the majority because of the failings and fallibilities of human thinking and memory, and because of the sheer bulk of factual knowledge now available. We are, moreover, under the stern injunction not to multiply entities "praeter necessitatem." Both lumping and splitting are excellent attitudes of mind under appropriate circumstances. The difficulty lies in judging which circumstances are appropriate. The writer holds that in the field of obscure endocardial diseases it is now a time for splitting, even if only into a number of temporary categories which fuller knowledge may enable some synthesizer to put together again.

There is another reason why the multiplication of entities is advisable at this stage, and that is that, in most parts of the world, these conditions are rarely seen and when one is seen there is a not unnatural tendency to identify it prematurely with a condition described by someone else, perhaps a senior and more experienced worker, and to force it, sometimes without adequate description, into a category into which it may not be tailored to fit and indeed into which it may not fit without gross distortion. Then these conclusions and descriptions are quoted back and forth without regard to their inadequacies. As a colleague has well put it,[1] "But there is a curious tendency, all too evident in the literature and in discussion on this subject, to gather uncritically into one group, and to quote as examples of a particular pathology, descriptions and case reports which have nothing really in common except their extreme obscurity; and which not infrequently (when the original source is consulted) prove to contribute only incomplete or inadequate data"! When to this confusion there are added names which imply the effect of certain etiologic factors when, in fact, the etiology is quite obscure, we have confusion worse confounded, and differences which may be of the highest significance are lost to sight.

THE NATURE AND BEHAVIOR OF THE MURAL ENDOCARDIUM

The nature and behavior of the mural endocardium is a much neglected subject, and we are extremely ignorant of many features of the endocardium. It was studied in some detail by Nagayo,[2] in 1909, and further study by modern methods is considerably overdue.[3,4] It is a considerably more complex structure than it might at first seem to be, and these complexities are rather glossed over in current textbooks. All the cardiac cavities are lined by simple squamous endothelial cells, very thin and tenuous, forming a complete continuous sheet which is only perforated by a considerable number of vascular channels. The endothelial sheet seems to be of a uniform nature throughout, but this delicate lining is supported by a framework of fibrous, muscular, and elastic tissue. There is a subendothelial layer of delicate collagenous fibers; underneath this is a rather thicker layer of collagen fibers strengthened by elastic fibers, and in this layer are lymph and blood channels. Under this there is a layer of smooth muscle fibers, probably but not certainly a complete layer and rather more plentiful in the atrial endocardium. The normal endocardium is thus a layered structure,

and has been regarded by critical microscopists as having from five to eight layers. Nagayo[2] distinguished five or six: (1) endothelium, (2) subendothelial layer, (3) connective tissue layer, (4) elastic tissue layer, (5) smooth muscle layer, and (6) deep connective tissue layer connecting with the vascular sheaths and containing the conducting fibers. This layer has the task of anchoring the endocardium to the underlying myocardium, from which the separation is usually quite distinct.

We can presume in view of the body's economy that this complex structure is necessary for the endocardium to fulfill its functions. Little seems to be known about the function of the endocardium taken as a whole, or about the functions of the individual layers. Throughout life the endocardium must be continuously varying its surface area under continually changing pressures. Presumably, the smooth muscle tone is continuously varying. The degree of change in the spatial configuration of the endothelial cells is unknown. Black-Shaeffer[5] has compared the functional role of the elastic fibers with that of the arterial internal elastic lamella, and thinks that in the normal heart the elastica plays an insignificant role, but, on the other hand, it may play a part in the recoil mechanism, as may the muscle layer. It may be that the adjustments made to stretch and recoil may differ in different areas of the endocardium, for, taken as a whole, the endocardium is not a uniform structure. It is thicker in the atria than in the ventricles, and in the latter there are important differences between the endocardium in the inflow tract and that in the outflow tract. In the inflow tracts the endocardium is thinner, more delicate, and with fewer collagen and elastic fibers; these are more abundant in the thicker, coarser endocardium of the ventricular outflow tracts. The layer of smooth muscle is very much less evident in the endocardium of the inflow tract and may not form a complete layer in these areas. The constancy of these differences in normal hearts suggests that they have some functional significance which may be dependent on pressure relationships, in that the outflow tract has to withstand higher pressures and greater turbulence than does the inflow tract, especially on the left side. Abnormal pressures and turbulence could be expected to result in changes in the structure of the exposed endocardium, especially if these changes in pressure are rhythmical and fluctuating.[6,7]

Before considering these changes, some further pertinent points may be mentioned. The endocardium is generally thought to be nourished and oxygenated directly from the blood in the chambers, so that we could expect the endocardium of the right heart to be less well oxygenated than that of the left, even though in other respects it is possibly better nourished. Moreover, the immediately subjacent subendocardial myocardium is also nourished from the chambers, as is revealed by the survival of some of these fibers following coronary infarction. But in the deeper subendocardial myocardium there is a vulnerable zone with a relatively poor supply of blood, lying in the watershed between areas nourished from the coronary arteries and that nourished from the cardiac chambers. This in abnormal hearts will be a shifting zone as nourishment from either system is impaired. Whereas these concepts seem to hold in general, it is not easy to see what purpose is served by the vascular channels which are actually in the endocardium itself, for in studying the capillary vascularization of the subendocardial

muscle layer in the human heart, Hecht[8] has shown that the capillary density of this layer is less than that of the myocardium generally, suggesting that this may be because this layer is partially supplied directly from the chambers. In part, this zone may be fed by offshoots of the arterioluminal vessels which connect the terminal twigs of the coronary vessels with the cavities, but the extent of this communication is not known and such vessels may enter into the endocardial blood supply. The functional significance of the long-known Thebesian veins is also not clear. Gregg and Shipley[9] showed, at least for the dog, that the coronary artery bed is drained by the superficial veins whose fields overlap and which anastomose widely and have a very big reserve capacity. They did not regard the Thebesian veins as an alternate system of venous drainage and, indeed, did not think these veins functioned as supply channels or as drainage channels; they are supported by Ozarai,[10] who regards these veins as a buffer system between coronary vessels and ventricles, and which may be emptied in either direction as required, having valves which can open either way and muscle fibers of a cardiac type in their walls.

Finally, it may be noted that the recuperative and regenerative power of the endothelium and of the endocardium is not well understood. Altschul[11] takes a poor view of the reparative power of the endothelium generally, and is supported in this view by Poole and co-workers[12] for the aortic endothelium (in the rabbit). These workers showed that a denuded area is covered by platelets but that large thrombi do not develop. Endothelial cells multiply and gradually cover the defect, but even after seven months they had not completely covered a small denuded area. Whether the endocardial cells are capable of more rapid regeneration is not known, but seems doubtful; taken as a whole, repair in the endocardium must be quite a complex process.

ISOLATED ENDOCARDIAL THICKENINGS

Isolated endocardial thickenings are well known and illustrate the effects of jets or eddies or of unusual turbulence upon the undamaged endocardium. They may occur as isolated or diffuse patches or as pockets, the so-called Zahn-Schmincke pockets, in which case the opening of the pocket is against the direction of the jet. Descriptions of these have been given by Saphir,[13,14] who has reviewed the older literature. Microscopically, these patches are local areas of fibroelastotic proliferation, and when a pocket forms, it resembles in miniature a normal heart valve, the endothelial cells are unaltered but the subendothelial layer is thickened, the collagen is hyalinized, the elastic lamellae are increased and extend into the walls of the pocket if one is formed, but in neither the patches nor the pockets is there any apparent increase in the smooth muscle fibers. It should be noted that there is no inflammatory change at all.[15,16]

Thus, these lesions would appear to represent in their purest form the structural endocardial changes consequent upon abnormal pressure stresses.

EFFECTS OF CARDIAC HYPERTROPHY AND DILATATION UPON THE ENDOCARDIUM

Little attention has been paid in recent years to the effects of cardiac hypertrophy and dilatation upon the endocardium. There seems to be little evidence

of any direct effect of hypertrophy upon the endocardium unless coronary insufficiency develops. But dilatation appears to have important effects. Domenici[17] showed that there was a hyperplasia of the collagenous and elastic fibers, especially in the left atrium, in response to a mechanical or stretching stimulus, but that where the myocardium was altered and the chambers became dilated, there was an evident hypertrophy of the endocardial smooth muscle cells. Fisher and Davis[3] showed that this enlargement of the muscle layer was most apparent in the outflow tract of the left ventricle. In their interesting study of endocardial thickening in the adult, they showed that it was most common in the left ventricle, that when mild, it was usually confined to the outflow tract, especially in the region just under the aortic valve, but if moderate or severe, it tended to involve not just the outflow tract but to appear diffusely over the whole endocardial surface, and did not correlate with hypertension, and only partly with the weight of the heart. These workers laid considerable stress on hypertrophy of the smooth muscle in these nonspecific forms of endocardial thickening, and they illustrate these fibers as lying interposed between elastic lamellae adjacent to the lumen. They also illustrate another band of elastic fibers below the muscle layer in the deeper visceral zone of the endocardium. Reference to Nagayo's scheme[2] given above will show that there is a discrepancy here, and that to his schema should be added a deeper elastic tissue layer which heightens the resemblance of the endocardial structure to that of the arterial wall.

Confirmation and extension of the work of Domenici[17] and of Fisher and Davis[3] is of importance, since it would appear that these workers have given us a means of distinction between endocardial thickening from eddies or jets, in which case fibroelastotic thickening alone is found, and from dilatation, in which case hypertrophy of elastic tissue and hypertrophy of smooth muscle are the dominant lesions. If so, this is important in relation to the contentions of Black-Shaeffer[5] that cardiac dilatation is of great importance in the genesis of at least one form of endocardial fibroelastosis of infancy, although unfortunately in his article he did not deal specifically with the response of smooth muscle.

ENDOCARDIAL FIBROELASTOSIS OF INFANCY*

A considerable literature has now grown up around the condition of endocardial fibroelastosis of infancy, which has been the subject of numerous reviews. Therefore, only certain aspects will be mentioned. It would seem that at least three varieties can be distinguished: (1) that in association with a variety of congenital cardiac defects; (2) that associated with a wide variety of metabolic defects or unexplained diseases, e.g., Hunter-Hurler syndrome,[18] epiloia,[19] glycogen-storage diseases,[20] and with a condition of generalized cystic lymphadenopathy and rash,[21] and with calcification of the coronary arteries[22]; (3) that which presents as a familial disease of unknown etiology.[23]

As might be expected, there are a series of different patterns which the endocardial fibroelastosis may present and in the associated features. Thus, Andersen

*I am most grateful to pathologists in numerous countries through whose kindness I have been privileged to see more than one hundred cases of this condition.

and Kelly[24] have drawn attention to four important features: that some endocardial fibroelastosis is found somewhere in the majority of cases of congenital malformation of the heart, that with the same defect the same areas of the endocardium will be involved, that the areas affected are those in which there is a local or generalized increase in pressure, and that the lesions will increase with age and are progressive.

Certain other important features should be noted. There is generally an absence of evidence of inflammation, the left heart and especially the left ventricle are particularly affected, there tends to be a sharp distinction between the thickened endocardium and the underlying myocardium, and the myocardium is often free from defects. Exceptions to these statements do, of course, occur.

The group of cases in which fibroelastosis is associated with a congenital defect calls for little comment, save to note that where there is calcification of the coronary arteries or where there is an anomalous origin of the left coronary artery from the pulmonary artery, then myocardial ischemic damage may be severe, with replacement fibrosis, and the usual sharp distinction between the myocardium and the endocardium may not be evident. In considering the second and third groups, we may most profitably concentrate on the latter. Kelly and Andersen considered that these represented a group with the following features in common: the disease tended to be familial, there was gross enlargement and dilatation of the left ventricle, and the fibroelastosis increased with age and was most marked in the left ventricle. They suggested that some metabolic defect might have weakened the myocardium so that dilatation resulted, and fibroelastosis then developed as a secondary phenomenon. This brings the second and third groups mentioned above into line, in that the metabolic defects more distinctly specified might be expected to weaken the myocardium and similarly lead to dilatation and fibroelastosis. Indeed, the variety of conditions in which generalized infantile fibroelastosis in the absence of malformation is seen suggests a common pathogenetic mechanism.

If then these types of infantile endocardial fibroelastosis are a consequence of severe dilatation, then the other postulated causes can be disregarded, save in as much as they may affect the myocardium. Thus, the concept of fetal endocarditis has generally been abandoned as has the idea that it is primarily a collagen disease.[25] Anoxia[26] is probably more important as a possible cause of myocardial damage than as a directly noxious influence on the endocardium; whereas the theory of Stresemann[27] that it is an overgrowth of the endocardial anlage is more important conceptually than practically. The views of Kelly and Andersen[23] represent a return to the conceptions long held by German workers,[28,29] as has been shown by Black-Shaeffer,[5] who has brought a variety of interesting data in support of these ideas, and further supported them by a formidable armament of mathematical and engineering evidence. There is much evidence to support these conceptions, *inter alia* the great variations in the condition in the newborn, and the fact that when such cases do occur under the age of one month, there are usually severe valvular defects, that in siblings, later deaths are associated with more severe lesions, and that the correlation with hypertrophy, although imperfect, is marked. They fit in with the recent evidence[3,14] as well as with such

reports as that of Hubschmann[30] on endocardial thickening in the dilated hearts of patients with diphtheria.

Black-Shaeffer's concept[5] is that, accepting some initial myocardial weakness or inefficiency, the systemic pressure after birth falls entirely on the left ventricle, with resultant strain on the myocardium, which, if it is weak, undergoes both hypertrophy and dilatation, the latter causing increased tension in the endocardium, with resulting proliferation of elastic fibers, just as the response to increased tension in the walls of muscular arteries is reduplication and increase of the elastic lamellae. Black-Shaeffer does not deal with the response of smooth muscle, but this layer is increased in some cases,[31] and, indeed, Mosca and Parenzan[32] regard the presence of a firm layer of smooth muscle in the deeper zone of the endocardium as a salient feature of the condition.

It would follow that if an extra burden which caused dilatation were to be thrown on the right ventricle, a similar response might be seen. Thus, Neely[33] reported cases of endocardial fibroelastosis in the right ventricle, with hypertrophy, dilatation, and relative sparing of the left ventricle, in three children who developed interstitial pneumonia which was presumed to be of virus origin in early childhood.

The importance of these concepts is in the light that they throw on the mechanisms by which endocardial fibroelastosis develops in infants, as well in the hopes of prevention which they raise. No light is, of course, thrown on the original source of weakness in the myocardium in which there is no obvious metabolic disease. Nor do they tell the full story of the pathogenesis, which has been studied from a different angle by Still and Boult.[34] The latter authors were concerned chiefly with the fibrous tissue component, considering the three possibilities of simple fibrous tissue overgrowth, subendocardial necrosis, and fibrous replacement, or incorporation of fibrin coagulum.[35,36] Electron microscopic studies suggested that the main components of the fibrous tissue had the same characteristics as fibrin, thus further suggesting that part of the endocardial thickening was due to the incorporation of fibrin coagulum.

Endocardial fibroelastosis of infants is now a well-recognized condition. It has been discussed here not so much for completeness or for its inherent interest, but in order to lay the ground work for the discussion that follows. From the work here reviewed, some tentative conclusions can be drawn: (1) that eddy and jet effects, causing rhythmic fluctuant pressures, will tend to produce proliferation of elastic tissue; (2) that cardiac dilatation will produce endocardial fibroelastosis, together with hypertrophy of the layer of smooth muscle in the endocardium; and (3) that some of the fibrous reaction may be due to incorporation of fibrin coagulum.

Since there is nothing to suggest that these reactions would not occur in the hearts of children everywhere in the world where circumstances permit, it is not surprising that this condition in infants is of world-wide distribution.*

*I have seen specimens in European, African, Indian, and Chinese infants, and the condition has been reported in cats and dogs by Elliot and co-workers,[37] who kindly permitted me to examine their material.

ENDOCARDIAL FIBROELASTOSIS IN ADOLESCENTS AND ADULTS

It is when we consider adolescents and adults that difficulties arise. All who have considered such cases have suspected that there is a difference between the infantile and adult forms of fibroelastosis. Before proceeding it is necessary to apply strict criteria, and the term "fibroelastosis" in this review is restricted to those lesions in which there is the thickened fibroelastotic layer of endocardial proliferation as seen in infants, with or without the hypertrophy of the layer of smooth muscle. It is far from easy to apply these criteria strictly because of paucity of description, and this is especially true in considering hypertrophy of smooth muscle, because information is too often lacking.

Certainly, true fibroelastosis of a mild type is common in adults. The Zahn-Schmincke pockets have been mentioned, and more severe lesions are often seen as complicating factors in a variety of heart diseases. But severe forms are rare as an isolated condition, especially those in which the fibroelastosis per se is the cause of heart failure. Cases have been described in adolescence[39] and in adults.[38, 40-44] Such cases have been seen rarely in Uganda. The causes of these lesions remain obscure. The patients may represent the late survivors of endocardial fibrosis of infancy, or may be the late victims of a severe acute cardiac dilatation, or the victims of some progressive disease causing fibroelastosis. Such a disease certainly exists in Africa.

OBSCURE CARDIOPATHY OF SOUTH AFRICA.* "BECKER'S DISEASE"

Under the title "Cardiovascular Collagenosis With Parietal Endocardial Thrombosis," Becker and his associates[45] reported forty cases of a peculiar form of heart disease occurring in South Africa. This was amplified in some respects in a subsequent report of a seminar.[46] The title given was perhaps, in retrospect, rather unfortunate and has tended to obscure the more important aspects of a fascinating and mysterious disease.

It occurs at all ages and in all races in South Africa, and the course may be either acute and rapidly progressive or more chronic, with survival up to three years or more. In Europeans, the acute cases show bouts of pyrexia, leukocytosis, but not commonly an eosinophilia, multiple embolic accidents, and repeated episodes of heart failure from which rescue becomes ever more difficult. Africans may show a more chronic course but with similar episodes of recurrent heart failure. Over 75 per cent of the cases have infarctions, solitary or multiple and all bland, and the illness may start with an infarction. Both sexes are equally affected, the well nourished and previously physically fit and robust, as well as the malnourished.

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*I am grateful to Professor B. J. P. Becker and Dr. C. B. Chatgidakis, of Johannesburg, for their kindness in permitting me to see and examine their material and for discussing it with me. I have put my own interpretation on their material, and they are in no way responsible or committed by any expressions or opinions set out in this review. In view of the length of the alternative names given to this condition, it is here referred to for brevity as "Becker's disease." This honors its discoverer without involving etiological or pathogenic concepts.

At autopsy, the hearts are dilated but not necessarily hypertrophied, and a thin rippled layer of fibrin coagulum may cover the entire endocardial surface of the ventricles. There is a swelling of the endocardium, due to an acute mucoid edema, with the fibrin coagulum on the surface, there being a metachromatic staining reaction of the endocardium which is presumed to be due to the presence of a specific mucopolysaccharide. The lesions may be strictly focal, in the form of small endocardial polypi consisting of an area of mucoid edema with fibrin accumulations and sometimes with fibrinoid change. In the myocardium itself there is marked interstitial edema, a serous myocarditis, with degeneration of muscle fibers especially affecting the inner third of the myocardium with hydropic changes, granular degeneration of the myocardial fibers, and foci of basophilic change. Although no lesions were present in the major coronary vessels, in the myocardial arterioles and venules as well as in the arterioluminal vessels and in the Thebesian veins, there were focal endocardial swellings, often as polypoidal excrescences on thin stalks, caused by a combination of mucoid edema and fibrinous exudate, with fibrinoid change and sometimes with hemorrhages. Such hemorrhagic polypi could occur on the endocardial surface as minute dark spots. In addition to this verrucose angiitis, there were endothelial cell masses in arterioles and capillaries, with capillary dilatation and stasis, and, in rare cases, a diffuse necrotizing arteriolitis has been noted. The acute phase is followed by a reparative granulomatous phase, which may be disturbed by a fresh development of mucinous edema. A thrombus may be deposited on the damaged endocardium, and this is the source of the major emboli.

On the other hand, vascular lesions occur in other organs. Microemboli are seen to affect the glomeruli, and these may come from the endocardial thrombi or, more probably, from the small polypi in the blood vessels. The aorta and its vasa vasorum show focal nodular swellings and increased metachromasia. But a remarkable feature of the disease is that the intima of the pulmonary artery contains considerable numbers of giant cells, and similar changes may affect the hepatic veins.

The healing of these processes leads, in the heart, to the development of many eccentric subintimal cushions of connective tissue in the blood vessels of the heart, and to the development of fibroelastotic plaques in the endocardium. This fibroelastosis is never very severe, and consists of focal endocardial plaques at the apex of the heart, overlying the papillary muscles, in the atria, and on the endocardium of the outflow tract in the upper part of the interventricular septum. The pericardium and, it should be observed, the valves are unaffected, and the mural thrombosis in the heart is usually not very marked.

The cause of these remarkable lesions remains obscure and no exactly comparable picture appears to have been reported in the literature. Becker and his associates[45] tended to identify this condition, on the one hand, with Löffler's disease, and, on the other hand, with endomyocardial fibrosis as recorded from Uganda, and these identifications must now be examined.

LÖFFLER'S DISEASE*

Under this name, "endocarditis fibroplastica," Löffler[47] described cases characterized by a progressive heart failure refractory to treatment; a febrile course, a high persistent blood eosinophilia which tended to diminish before death, and multiple systemic infarctions due to emboli. At autopsy, the ventricles showed thickened, scarred endocardial surfaces on which thrombi had formed. Numerous similar cases have now been described[49-52] in the literature, although the reports are in many aspects rather confusing. Fortunately, Serenella Weiss-Carmine[48] has published a detailed review of twenty-six of the reported cases, and has complained of the inadequate recording and description of many of the cases, of insufficient examination, and of many obscurities in the presentations. It would be tedious to elaborate, and Weiss-Carmine's conclusions will alone be considered. She draws attention to the following points. First, the complete picture described by Löffler is not often seen, or if seen, has not been recorded in detail. The disease is recorded predominantly in males, there being only three females among the twenty-six patients reported upon. Twenty of the patients were in the age range of 30 to 50 years. The clinical course was marked not merely by eosinophilia and infarctions but also by evidence of the presence of a generalized vascular disease affecting the central nervous system, the kidneys, and many other organs, sometimes to such an extent that the degree of cardiac damage was not appreciated. Arteritic lesions were found in the smaller coronary vessels, in the vessels of similar size in the brain, kidney, spleen, liver, lungs, and adrenals, and in the intestinal wall. About half of the patients were febrile, and twenty-one of them had a leukocytosis. The valves were affected by a valvulitis, with vegetations present in six patients. In about a third of the patients the valves were drawn down by thickening and shortening of the chordae tendineae and their fusion to the mural endocardium. The endocardial thickening was a scarring, with only a few split or very irregularly growing elastic fibers, and the involved area was often covered by thrombi, from which emboli originated. There may be quite massive thrombosis with minimal involvement of the endocardium, as in Buchler's case.[53] The hearts are usually clinically enlarged, with a mitral configuration, and are usually found to be hypertrophied, weighing 400 grams or more. The inflow tract of the ventricles is involved, and although the inner third of the myocardium is maximally involved, the process may, and often does, spread to involve the whole thickness of the wall (Fig. 1). There may be, and indeed usually is, an intense eosinophilic infiltration of endocardium and myocardium.

The cause of this disease is unknown. There is no satisfactory evidence incriminating parasites as causative agents, but their presence has not always been satisfactorily excluded.[48] Most writers have suggested that this is primarily a disease of some altered sensitivity[54] due to some allergen, but the suspected allergen has not been identified.

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*I am grateful for discussions with Professor F. C. Roulet and Professor Uehlinger on Löffler's disease and endomyocardial fibrosis. Again, they have no responsibility for the views here expressed.

Comparison of Löffler's disease with Becker's disease shows that there are such marked discrepancies that they considerably outweigh the few similarities. Löffler's disease is a generalized arteritic disease in which the heart is affected, with damage to blood vessels, myocardium, and heart valves, and this results in severe endocardial scarring, with negligible fibroelastosis. Conversely, in Becker's disease a generalized arteritis has not been noted, the vascular changes being confined to the heart and the major veins and arteries; there is widespread cardiac damage, but this heals, not by scarring but by the development of fibroelastotic patches. The clinical course of the patients with these diseases is widely different, and the eosinophilia in blood and tissues, so marked a feature of Löffler's disease, is not a feature of Becker's disease. We can now take a look at how the lesions seen in these two conditions compare with endomyocardial fibrosis as observed in Uganda.

ENDOMYOCARDIAL FIBROSIS IN UGANDA

The heading is not meant to imply that the disease is confined to Uganda; indeed, it is now clear that it occurs in many tropical countries,[55,56,58] but the statements made herein are based on the observations made in Central Africa.[57-63] Endomyocardial fibrosis is a common disease which is responsible for about 15 per cent of all deaths from cardiac failure in the last fifteen years in Mulago Hospital. It affects both sexes equally and has occurred in patients of from 4 years to over 70 years of age. So far, all the cases have occurred in Africans, and no case has been recognized in an Indian or European resident in Uganda. Not all patients develop cardiac failure, and in some instances, quite severe lesions have been found in patients dying from unrelated conditions. Those dying with heart failure exhibit a variety of clinical features which are found to correlate quite closely with the pathologic changes noted in the hearts at autopsy. These clinical features have enabled a confident clinical diagnosis to be made in many cases with subsequent autopsy confirmation. The clinical diagnosis will not be discussed in detail, because this has been dealt with elsewhere.[57,62]

Briefly, patients may present as cases of heart failure without any distinguishing features, or with evidence of incompetence of one or both A-V valves, usually the mitral, or they may present with a picture quite like that of constrictive pericarditis.[64] Much more rarely there may be a very large hydropericardium or stenosis of the mitral or tricuspid valves. The course is slowly progressive, with poor response to treatment, without pyrexia or episodic heart failure, and with survival for rather longer—four years or more—when the right ventricle is involved. Eosinophilia in the blood is inconstant, and usually due to tropical parasites; it is never as marked as in Löffler's disease, and in the tissues, including the heart muscle, any eosinophilia is very uncommon.

Certain clinical features deserve emphasis—the nonepisodic nature of the disease, the absence of pyrexia and any evidence of infection or allergy, the utter lack of evidence of any generalized vascular disease, and, particularly, the great infrequency of embolic accidents.[64] Embolic accidents have been very rarely

seen in the cases in Uganda (comprising well over one hundred autopsies), and such as have occurred either are due to a terminal bacterial endocarditis or are massive terminal infarctions involving major blood vessels. This lack of embolic accidents is a striking phenomenon, marked not only in the cases occurring in Uganda but in cases which appear to be similar in Europeans elsewhere.[65] Similarly, at autopsy, there has been a striking lack of lesions in organs other than the heart, except for the changes of congestive failure or of specific conditions unrelated to this form of heart disease. This is quite unlike Löffler's disease; nor have the changes in the intima of the large vessels, such as are seen in Becker's disease, been found in endomyocardial fibrosis.

Fig. 1.—Transverse macrosection of heart of an African adult male. In life, heart failure, multiple emboli, cerebral and renal symptoms. At autopsy, massive endocardial thrombi, scarring in whole thickness of ventricular myocardium, fibrosis of endocardium and myocardium with intense eosinophilic infiltration. No evidence of parasites. This represents the only African case I have seen which apparently shows all the lesions of Löffler's disease. Unfortunately, the heart was destroyed in an explosion, preventing further detailed study.

At autopsy, the hearts may be found to be enlarged and dilated, but more typically they are small and contracted. The weight of the hearts has varied from 170 to over 500 grams, but the weight of the heart of the Uganda African is less than that of the European[66]; it is, however, certain that, in general, there is no evidence of hypertrophy. A characteristic lesion is a depressed rugose area or a sulcus over the apex of the right ventricle or, less commonly, at some distance

up the right ventricular wall, and wherever this is present, it is sure evidence of severe damage to the right ventricular endocardium. Often, such apical recession is accompanied by considerable dilatation of the conus and infundibulum.

When the heart is opened, any or all of the chambers may show endocardial lesions, but the ventricles are always most severely damaged and show the major lesions. The total incidence of involvement of the ventricles is about equal, but the most extensive damage is in the left ventricle, although the lesion in the right ventricle may be such as to lead to obliteration of the apical cavity (Fig. 2) and the filling of the cavity with a mass of clot and fibrous tissue in various stages of organization up to complete fibrosis, and this is the cause of the apical recession visible externally. The effective cavity may be converted into a small saucer-like depression in which the papillary muscles stick up like a small marble pillar (Fig. 3).

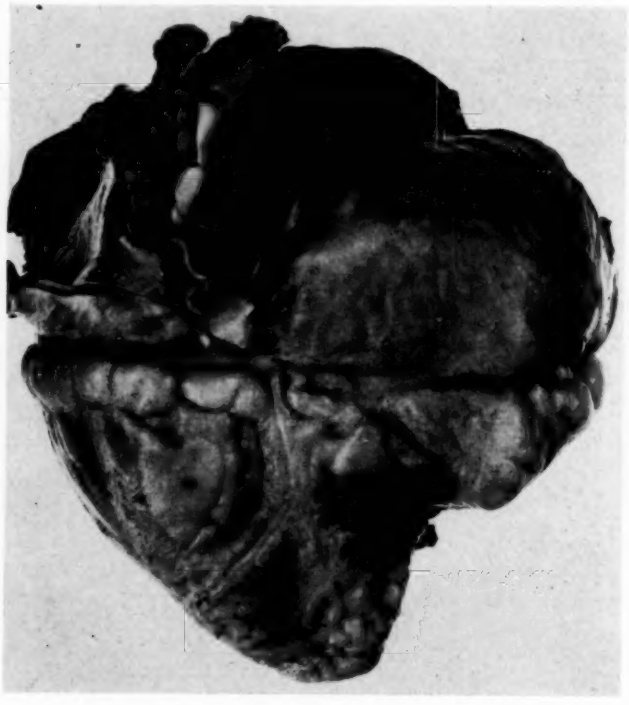

Fig. 2.—Endomyocardial fibrosis. Posterior view of heart, showing the external recession of right apex, with internal ventricular apical obliteration.

More usually, however, the A-V valves are drawn down by the shortening and thickening of the papillary muscles and chordae tendineae, and by their posterior cusps becoming adherent to the fibroplastic lesions on the underlying walls of the ventricle (Figs. 4 and 5). The more extreme lesions of this type involve the mitral valve, and the posterior cusp may completely disappear, being marked only by a slight ridge and by white columns of fibrous tissue which mark the fused remnants of the valvular apparatus (Fig. 6). The valves show no evidence of valvulitis and seem affected only in the way described, although there

may be a terminal bacterial endocarditis affecting the valves or the mural endocardium. The pulmonary and aortic valves seem never to be affected, and, as will be described, the scarring process always stops short some distance from the semilunar valves.

The endocardial lesions are of two types. The first and basic lesion is a deep scarring of the endocardium of the inflow tract, which usually involves the apex and spreads upward, especially on the posterior wall, to behind the posterior cusp of the A-V valve. The papillary muscle and the chordae may be partially or completely covered with fibrous tissue. There may be a continuous sheet of fibrous tissue from the atrium, flowing over the posterior cusp of the A-V valve and covering the apex like an inverted candle snuffer, or there may be separate patches. The lesion rises only a short distance on the septal wall and often terminates sharply, with a thick, rolled ridge of white fibrous tissue. Thus, this type of lesion affects and is confined to and delineates the inflow tract. The endocardium may be a pearly white color, thick and with a rugose surface, or it may

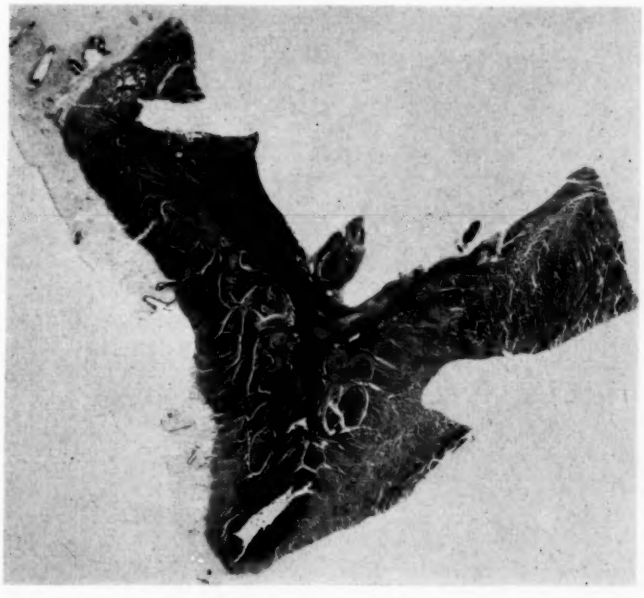

Fig. 3.—Endomyocardial fibrosis. Macrosection of right ventricle, showing external recession and internal obliteration.

be stained a brown or greenish color, or covered with a layer of thrombus which may be slight but is sometimes so massive as to fill the cavity. There may be large atrial thrombi. The thickened endocardium is not sharply delineated from the underlying myocardium but merges with it, and tongues of fibrous tissue extend into the inner one third of the myocardium, which may show, macroscopically, dilated blood vessels in the subendocardial region.

The second and minor type of endocardial lesion is a fine white filminess which is visible on the endocardium adjacent to the semilunar valves. It is always a white opacity, thin, with indefinite margins and never covered with thrombus,

and it is sharply delineated from the myocardium. Section shows that this lesion is a moderate fibroelastotic proliferation of the endocardium, and it would seem to represent only an endocardial reaction to the altered hemodynamics of the ventricles. It is the only lesion in these cases in which there is marked and regular elastosis.

Fig. 4.—Endomyocardial fibrosis, showing apical involvement of left ventricle and spreading up to involve posterior leaflet of mitral valve. Note degree of adherence.

Microscopically, the endocardium of the inflow tract shows the presence of a thick layer of hyalinized fibrous tissue overlying a tangle of looser textured collagen fibers. The superficial zone is usually acellular and may, as stated, be covered with thrombus, which may be partially incorporated. The deeper zones contain a few cells, usually lymphocytes, macrophages, and plasma cells, and in the zone in which the fibrous tissue joins the myocardium there is invariably a fine layer of granulation tissue with a few inflammatory cells, but this zone is always small in extent. Tongues of fibrous and granulation tissue extend into the myocardium, and in them are always large dilated blood vessels, presumably Thebesian veins and arterioluminal vessels with normal endothelial cell linings. There is no evidence of any verrucose angiitis such as is seen in Becker's disease. All cases show a degree of fibrosis of the myocardium which is not related to the coronary vessels but to the communicating vessels, and which rarely extends in deeper than one half of the thickness of the wall. Involvement of the whole

thickness of the ventricular wall has not been seen in endomyocardial fibrosis, in contrast to the changes often seen in Löffler's disease. No changes are seen in the major coronary arteries, but in cases in which there is very marked endocardial scarring, the small arterioles may show a degree of obliterative change not evident when the lesions are mild.

Fig. 5.—Endomyocardial fibrosis. Macrosection of left ventricle, showing the depth of involvement of the myocardium.

Microscopically, the myocardial fibers show a variety of lesions, present in all areas in the inner third of the myocardium but most marked in areas adjacent to the damaged endocardium. The fibers are commonly thin and atrophic but with the nuclei enlarged, very square-ended, and hyperchromatic. There is often a wavy loss of sarcoplasm, but many fibers show varying degrees of interfibrillary edema, often with large watery vacuolation. There is often interstitial edema, but no abnormal materials have been seen, and there is no mucoid degeneration or basophilic change. There is little or no cellular infiltration of the myocardium, no parasites have ever been identified, and hemorrhage and frank necrosis are not seen, nor is there any abnormal pigmentation. There may be calcification of the fibrous tissue, either on the heart wall or in the valves, and this may be recognized radiologically during life. No lesions resembling active or healed Aschoff bodies have been encountered, save in a few instances in which there was a valvulitis and involvement of the aortic valve suggesting the presence of a concomitant rheumatic carditis. Such instances have been very few in pa-

tients in Uganda; the association may be more frequent in Nigeria.[67] Saphir[68] has recently emphasized the necessity of adhering to strict criteria in the definition of an Aschoff body, but even when one adopts somewhat less stringent criteria, there is no evidence of rheumatic lesions in the vast majority of cases of endomyocardial fibrosis.

Fig. 6.—Endomyocardial fibrosis. Left ventricle, showing shortening of chordae tendineae and distortion of posterior mitral cusp and clot at base of papillary muscle. Note sparing of outflow tract in this and in Fig. 4.

The amount of elastic tissue in the lesions of the inflow tract is small, and the fibers are broken up and irregularly scattered. No fibroelastotic proliferation at all is seen in the vast majority of cases, and although there may be a mild fibroelastotic proliferation in the outflow tract, this, as indicated above, is regarded as secondary. A few scattered remnants of elastic fibers may serve as markers of the original endocardium. The layer of smooth muscle is either destroyed or absent, or present only in fragments; it is never hypertrophied. Thus, as Thomas and associates[41] have emphasized, the lesion in endomyocardial fibrosis is a destructive lesion of the endocardium and of the subjacent myocardium, with scar formation. In this respect, and in the consequences which result from such widespread scarring of the ventricular inflow tracts, it resembles Löffler's disease. It cannot be too strongly insisted that in endomyocardial fibrosis and

in Löffler's disease the scarred areas of the endocardium do not show fibroelastotic proliferation.

Such fibroelastosis as does occur is confined, as has been stated, to the outflow tracts below the semilunar valves, especially in the subaortic region, and presents as typical mild fibroelastotic proliferation without hypertrophy of smooth muscle, without any evidence of inflammation or of a granulation tissue layer, and without any extension into the undamaged myocardium underneath, thus differing in every respect from the scarring and repair seen in the endocardium of the inflow tract. These fibroelastotic lesions, which occur in the right outflow tract usually as small diffuse patches, are interpreted as compensating endocardial thickening due to altered pressures, jet or eddy effects, and are completely unlike the destructive reparative lesions of the inflow tracts.

The absence of constant extracardiac pathology, of generalized arteritis, has been mentioned. No constant changes in blood or body fluids have been found, and no constant association with parasitism noted. Giant cell internal arteritis of the pulmonary artery is not seen, and there are no constant lesions in the aorta, although in many cases there is a degree of aortic hypoplasia which is a common finding in East Africans at postmortem.[69]

COMPARISON OF THESE VARIOUS DISEASES

Comparison of these various diseases—Becker's disease, Löffler's disease, and endomyocardial fibrosis—shows that the detailed distinctions between them are far greater than their few similarities. Indeed, obscurity is their main feature in common. The main features of these conditions are compared in Table I, and detailed comment would be superfluous. Whenever these diseases have been critically compared,[41,46,48] the conclusion has always been reached that they are quite separate and quite distinct clinical and pathologic entities, distinct from each other and distinct too from endocardial fibroelastosis in every sense in which that term can be applied to a specific disease entity. They are all uncommon diseases of obscure etiology, and their pathogenesis is known only in part. There is nothing to be gained at this time, save ease of memorizing, in lumping them together while in the present state of uncertainty. There is much to be said for using eponymous or purely descriptive labels which do not imply etiologic theories. The etiology is not likely to be elucidated if, indeed, they are all lumped together, and will be lost in such terms as "adult fibroelastosis." Indeed it is notable how writers who have confused these entities all come to imply that they are dealing with a disease of multiple etiology. The probability is otherwise; they are likely to be diseases of specific etiology, in the accepted sense of that term.

GEOGRAPHICAL DISTRIBUTION OF THESE DISEASES

Uncertainties of classification make it premature to discuss in detail the geographical distribution of these diseases.

Becker's disease seems so far to have been recorded only from South Africa, but personal information leads me to suspect that it occurs in Malaya and the

TABLE I. COMPARISON OF BECKER'S DISEASE, LÖFFLER'S DISEASE, AND ENDOMYOCARDIAL FIBROSIS

	BECKER'S DISEASE	LÖFFLER'S DISEASE	ENDOMYOCARDIAL FIBROSIS
Clinical			
Age	All ages	Adults	All ages
Sex	Equally affected	Gross male predominance	Equally affected
Nature of Disease	Episodic	Progressive	Progressive
Pyrexia	Bouts of pyrexia	About one half show pyrexia	Usually afebrile
Leukocytosis	Common—usually not eosinophilic	Eosinophilia (may disappear terminally)	Leukocytosis uncommon as is eosinophilia
Infarctions	Common—bland	Common. Severe	Rare
Nonembolic Extracardiac Lesions	Kidneys	Brain, kidneys, lung, spleen, adrenal, intestine, etc.	Nil
Type of Disease	Nonvalvular heart disease	Mixed type with valvular lesions	Usually valvular
Anatomical			
Pericardial Effusions	Common	Variable	Usually absent
Pericardial Recession	Nil	Not described	Common
Myocardium: Depth of Lesion	Inner one third	Inner third——→Full thickness	Inner one third to one half
Endocardium: Area Involved	Apex ventricle, papillary muscle, outflow tract	Variable—chiefly inflow tract	Confined to inflow tract
Acute Lesion	Mucinous edema	Destructive eosinophilic degeneration	Destructive lesion ? nature
Late Lesion	Fibroelastosis	Scar tissue. No elastosis	Scar tissue. No elastosis
Thrombus	Variable. Usually moderate	Severe	Variable
Old Endocardium	Recognizable	Destroyed	Destroyed
Heart Size	Large, 340 to 795 grams	Large, over 400 grams	Very variable, 150 to over 500 grams
Hypertrophy of Ventricles	Usual	Usual	Not usual
Cell Infiltrate	Moderate	Severe	Minimal
Large Coronary Vessels	Normal	Normal	Normal
Small Vessels	Verrucose angiitis	Periarteritis and endarteritis	No lesions (obliteration late)
Right Ventricular Obliteration	Nil	Not specified	Common
Aorta	Focal intimal swellings	Nil	Nil
Pulmonary Artery	Giant cells in intima	Not specified	Nil
Renal Lesions	Microemboli	Marked arteritis	Nil
Brain Lesions	Infarcts	Infarcts and arteritis	Nil
Cause	Unknown ? Infection altered sensitivity	Unknown ? Altered sensitivity	Unknown ? Nutritional ? Infective

Far East, and perhaps the case reported by Khaira[79] is an instance of this disease. It probably occurs in other areas of Africa, although having seen Becker's material, I cannot recall having seen such a case in Uganda. The lesions are so striking that they should be recognizable.

It is more difficult to separate out Löffler's disease and endomyocardial fibrosis, particularly in the descriptions in the older literature. Endomyocardial fibrosis seems to occur all over tropical Africa, from the Gambia to the Indian Ocean, but is not frequent in the Rhodesias and is not recorded from South Africa. It occurs in Ceylon[55] and in Southern India,[56] and has been reported from Malaya,[70,71] from Oceania,[72,73] and apparently from Hawaii.[74] I have personal knowledge of several cases in men who were prisoners of war in the Far East. Undoubted cases have been reported in England, and again I have knowledge of others, as in the United States,[75,76] but it is difficult to decide on the basis of many existing reports. The cases described by Edge[77] and Grey[78] seem, in retrospect, to be cases of Löffler's disease. This has been chiefly reported from Western and Central Europe, although a case has been reported from England,[54] and more recently one from the United States.[52] But the difficulties in interpretation make definite statements hazardous until more information is available. It is important that more precise identifications be made, because study of the geographical distribution may point to etiological factors. The importance of these is manifest when a disease which is known to cause endocardial lesions and to be due to a specific parasite is considered, namely, Chagas' disease.

CARDIAC LESIONS OF CHAGAS' DISEASE

It is to be hoped that the writer, a pathologist in Africa, will be forgiven for dealing with a condition with which he has little acquaintance and which does not occur in Africa. But it has many aspects of particular importance. In the acute stage of the disease, the *Trypanosoma cruzi* causes a parasitic pancarditis with lesions in the endocardium and epicardium, although the primary lesion is a myocardial one. The parasites invade the myocardial fibers, multiply intracellularly, break down the cell, and are liberated in the interstitial tissue so that edema, cellular infiltration, and fibrosis develop.

Endocardial lesions are more common in the late stages of the disease. There is often widespread bodily disorder, with gross dilatation of esophagus, colon, and ureters due to parasitic destruction of the ganglia. The cardiac lesions have been described by Laranja and associates.[80] Sudden death may occur, with or without previous heart symptoms, which include those of tachycardia and various arrhythmias, often with heart block. In all cases the hearts are hypertrophied and dilated, and weights of over 500 grams are common[81]; the dilatation affects the right chambers especially, whereas the left ventricular wall is usually markedly hypertrophied, save when an aneurysmal thinning occurs. Circumscribed patches of endocardial fibrosis occur, usually at the apex but also at the base, or in both sides. Much less frequently is there endocardial fibrosis on the right side. Mural thrombi may be present, especially where there is endocardial fibrosis. In about a third of the cases, thinning of the left ventricular wall develops, with the

formation of an aneurysm or pseudoaneurysm. In all cases there was a myocarditis with a heavy cellular infiltration, and inflammatory cells were plentiful in the epicardium and the endocardium. The muscle of the septum was particularly severely involved. There was considerable diffuse fibrosis of the myocardium, particularly in the left ventricle, probably in part the result of ischemia from obliterative changes in the coronary vessels. The aorta is commonly atherosclerotic.[82] Embolization from the mural thrombi is not uncommon and rupture of the cardiac aneurysms is often seen. In all of the cases described by Laranja and associates[80] the leishmanial forms of *Trypanosoma cruzi* were found.

This represents then a parasitic disease of the heart in which endocardial lesions are common, but it shows very great differences from the appearance described in the three obscure heart diseases discussed above. It is naturally limited to the areas in which the parasite exists. The descriptions of the cardiac aneurysms are, however, reminiscent of the ruptured aneurysms of the left ventricle in young people described many years ago from West Africa,[83] although similar cases were not recorded from the same area in a more recent study,[84] and no similar cases have been described from elsewhere in Africa. There has been suspicion that parasites might account for the lesions of Löffler's disease, but nothing has ever been proved, and it is unlikely that they are direct causative factors in endomyocardial fibrosis or Becker's disease. Certainly there is an abundance of possible parasitic causes in Africa. Filaria are not known to cause heart disease, but African trypanosomiasis can cause a myocarditis in human beings, and extremely severe lesions in monkeys.[85] Cardiac toxoplasmosis has been described,[86] but Toxoplasma or similar organisms have not been found in endomyocardial fibrosis or in the other obscure heart diseases. Although parasites may be concerned in the etiology of these diseases, it does not appear that they do so by direct action on the heart. Moreover, our difficulty in ascribing these diseases to parasites is the curious localization of the disease in the heart, a localization suggestive of the involvement of metabolic factors.

OBSCURE HEART FAILURE WITH MURAL THROMBOSIS

There are very many reports in the literature[87-94] of cases of obscure heart failure with mural thrombi in the ventricles, either without underlying endocardial fibrosis or with only a mild lesion, the apparent result of early organization. About many of these cases there hangs a vague aura of malnutrition or of metabolic defect[95,96] or intoxication,[97,98] most marked perhaps in the case reports from South Africa,[99,100] in which it appeared that episodes of heart failure could be relieved by improved diets, with relapse on return to the patient's normal poor diet. Once this is said, the question of cardiac beriberi looms up. The fulminant form of cardiac beriberi has been well described in its clinical aspects. The onset is sudden, there are no arrhythmias, the right heart is chiefly affected, and dramatic improvement follows the administration of thiamine, an improvement so dramatic that it can be used as a therapeutic test.[101] The pathologic changes have been less well described, at least in the English literature; the heart shows dilatation, particularly of the right side, there is no endocardial lesion or mural thrombosis, and the myocardial fibers are swollen and show a

watery vacuolation with interstitial edema, and with an absence of anything to suggest myofiber necrosis and with no inflammatory infiltration.[102] The subendocardial region is not specifically affected.

But is there such a thing as chronic cardiac beriberi? It seems not to be recorded in areas in which acute beriberi exists, and if the usual explanation of the acute beriberi lesion as a "biochemical lesion" is accepted, it seems doubtful whether such an entity could exist. But there are many reports, mostly emanating from the heyday of the vitamin era of the so-called "occidental beriberi" usually associated with alcoholism. The criteria laid down for the diagnosis of this condition, as Follis[103] has wittily pointed out, are not very sensible, there being a tendency to ascribe this diagnosis to a medley of obscure cardiac diseases whose only common feature is a failure to respond to any form of therapy, including vitamin administration! Many patients are alcoholics, and evidence of liver disease is commonly found.[104] The changes recorded in the hearts of these patients include enlargement due to dilatation and hypertrophy, multiple mural thrombi usually in the left ventricle, with frequent systemic emboli and little or no endocardial fibrosis, although some of the thrombi may show partial organization. The thrombi are usually at the apex or in the inflow tract.

The underlying changes in the myocardium are variable and fall into four main groups: (1) There may be no recognizable histologic abnormality. (2) There may be a true myocarditis, with myofiber death and a cellular infiltrate in which macrophages, lymphocytes, and plasma cells are more prominent than polymorphonuclear or eosinophil cells. These changes may be focal or diffuse. (3) There may be myocardial fibrosis, diffuse or focal, often perivascular, with some evidence of organization and a mild inflammatory cell infiltrate. Some of these may represent the later reparative stages of the changes of Group 2. (4) There may be a hydropic degeneration of cardiac muscle fibers, with a watery vacuolation, separation of myofibers, hyaline degeneration, nuclear enlargement with hyperchromatism, and interstitial edema. Cellular infiltration is minimal, and the lesions are often most marked on the right side and in the subendocardial myocardium.

About the first type, little can be said, although it is well recognized that heart failure can occur without recognizable changes in the myocardium. The changes listed in Groups 2 and 3 occur not infrequently, and probably represent some forms of infective myocarditis of unexplained etiology. Thanks to the reports of many investigators, notably Saphir[105] and Lyon,[106] we know that true myocarditis is common in a host of specific diseases. Some of these are geographically restricted, such as leptospirosis,[107] which can cause a severe myocarditis but does not occur in East Africa, whereas others, just as capable of causing myocarditis,[108] are ubiquitous in the tropics, such as viral hepatitis. Some may cause persisting lesions in the heart, e.g., typhus, whereas others, such as plague, are notorious for causing heart failure after the acute phase is over, if the patient exerts himself. Cardiotropic viruses capable of causing severe cardiac damage are common in the tropics, e.g., E. M. C. virus, and severe degrees of myocarditis are not uncommon both in man and animals. Indeed, few Africans in Uganda die of an infectious disease without there being some myocarditis.[109]

In many of the cases of obscure heart failure, with or without mural thrombus, the onset of the disease dates from some febrile episode, although in others there is no obvious point of onset.[110-112] The course may be long or short, but what makes many such cases difficult to interpret is the discrepancy, so often commented on, between the clinical signs and symptoms of heart disease and the autopsy findings.[110] In a patient with a plethora of signs and symptoms there may be minimal cardiac lesions, whereas another patient will show massive lesions when there have been minimal indications of cardiac disease in life. It is, however, one thing to suspect a specific etiology in a case of myocarditis,[112,114,115] or obscure cardiomyopathy,[113] but quite another thing to prove it, particularly in an autopsy specimen, and the infectious causes of many cases of myocarditis will remain obscure unless elaborate examinations beyond the scope of less well-equipped centers are carried out. Where a specific myocarditis does affect the endocardium, it may be assumed that this is usually through a direct extension of the infectious or inflammatory process, and that thrombus will be deposited directly on an inflamed surface, probably with rapid accretion, inadequate fixation, and great liability to detach and cause embolic accidents. In most such cases, however, the myocardial damage is generalized and diffuse, with no special involvement of the subendocardial layer. This particular localization is such a feature of endomyocardial fibrosis, of Becker's disease, and, to a lesser extent, of Löffler's disease, and renders it somewhat unlikely that a specific infectious agent is concerned, although some viruses do tend to attack the subendocardial myocardium.[109,116]

When we turn to the cases of Group 4, those with myocardial hydropic degeneration, we enter into the great "terra incognita" of cardiac pathology, for as Cameron[117] has said in his monumental work, *The Pathology of the Cell*, "no more disputed instance of tissue cell disturbance is known . . . than hydropic change," and he points out that the challenge has not yet waked sufficient response from histologists. He points out that the change known as watery vacuolation is only an early stage of full-blown hydropic degeneration, and that, if the conclusions of the cytologists are accepted, then a cell begins to show watery swelling as soon as irreversible processes leading to death set in. Thus, hydropic degeneration must represent a severe alteration and perhaps is evidence of cell death.[118] Certainly, as Cameron says, and as is so clearly visible in the myocardial fibers, hydropic changes are associated with nuclear disturbances and go on to necrobiosis. In a further review,[119] he has shown how, in certain specialized cells, at least, hydropic change is a clear indication of profound alterations in cell chemistry due to mitochondrial damage. There is no reason to suspect that the specialized myofiber is not affected in the same way, and it is easy to imagine how the hydropic degeneration of beriberi, with its biochemical lesion, could come about and also how it could cause fulminant heart failure. It is not so easy to visualize the sequence of events in the more chronic forms of heart disease. The hydropic degeneration could be a terminal event. In which case, what are the lesions of the protracted stage? Can myofibers just disappear without inciting an inflammatory response? Can they more easily do so if they undergo hydropic degeneration before they die? The particular vulnerability of the sub-

endocardial myocardium could be explained on the basis of its poorer blood supply. If hydropic changes are irreversible, then necrobiosis should follow, with inflammatory reaction and fibrosis. This sequence of events has been postulated in endomyocardial fibrosis and could explain the myocardial fibrosis, but why should the endocardium be damaged and particularly the inflow tract? Why should mural thrombi develop? At present, we have no answer to these questions. We know very little of the effect of nutritional disturbances on the heart, and what is known is difficult to interpret. Certainly, myofiber necrosis can be caused by malnutrition, because potassium deficiency can cause such lesions with a marked inflammatory infiltrate,[120] and so can thiamine deficiency in animals. But when both potassium and thiamine are deficient, there are no cardiac lesions, but areas of necrosis in skeletal muscle.[121] Selye[122] has devoted much attention to the production of cardiac muscle necrosis by chemical means, by manipulation of the mineral and adrenal corticosteroid balances, and has shown that a lesion similar to endomyocardial fibrosis can be produced in the rat by experimental means.[123] It is difficult to be sure of the relevance of this to the human disease. The Uganda African tends, on the whole, to be mineral deficient and to have relative underactivity of the adrenal cortex.[124] It does, however, point to the importance of concentrating on the nutritional and metabolic factors in the etiology of these uncommon forms of heart disease, and it is clear that if we knew more about the causes, effects, and natural evolution of the watery vacuolation of myocardial fibers, our understanding of heart disease would materially increase.

MURAL THROMBOSIS

There is a curious discrepancy between the frequency with which mural thrombi give rise to emboli in the cases of obscure heart disease without endocardial fibrosis and the infrequency of these events in cases of endomyocardial fibrosis, both in Africans and Europeans.[65] To some extent this is a feature of Becker's disease and Löffler's disease, but not so markedly as in endomyocardial fibrosis. It would appear not to be a racial factor. The liability to intravascular clotting appears distinctly less in the African than in the European,[125] and is a marked feature in the Uganda African, whose liability to postoperative thromboembolic phenomena is very slight. The basis for this is not clear and has not been elucidated by studies so far carried out in Uganda,[126,127] but clearly has very great importance for the problem of coronary thrombosis so rarely seen in the Uganda African. The infrequency with which embolic accidents occur in Europeans with endomyocardial fibrosis similar to that seen in Uganda Africans suggests that this is inherent in the nature of the disease process itself, rather than in the blood, but it raises the whole question of the relationship between endomyocardial fibrosis of the Uganda type and the cases reported, notably in the American literature, of endocardial fibrosis and mural thrombosis in which emboli occur. Are these the same disease, with greater severity in the African cases so that the hearts are relatively more immobile, or are they related to the speed of progression of the disease, or the degree of adhesion of the thrombi, or to more active endothelization, or to some property of the clots themselves?

These questions can be raised but they cannot at present be answered satisfactorily. Indeed, can cardiac dilatation and relative immobility itself lead to clotting, as has been suggested in the South African cases,[100] or must there be endocardial damage before a clot can form? What is the nature and explanation of the sudden massive postoperative clotting in the heart that Letac and associates[128] have reported from Dakar?

One way of explaining the relative paucity of embolization in endomyocardial fibrosis is suggested by the now well-established work of Magarey,[35] who showed that irregularities of the endocardium lead to fibrin-skimming, with fibrin accretion and incorporation on the surface, and subsequent thickening of the endocardium, a relatively slow process and one in which large thrombi might not form until late in the disease, more or less as coincidental lesions. This could certainly explain some cases and could explain how in certain instances of endomyocardial fibrosis an old thrombus is completely walled off by thick white acellular hyaline fibrous tissue, "thrombagenous parietal endocardial fibrosis," as Hertel[129] called it, but it seems doubtful whether it could explain all cases. One other thing is suggested by this and is supported by other evidence, that is that the essential lesion in endomyocardial necrosis is primarily a myocardial lesion, probably starting in the subendocardial lesion, and secondarily, and mildly, involving the endocardium—a pointer perhaps to a nutritional metabolic cause.

However, it must not be forgotten that in some cases an endocardial thickening can occur from direct damage, presumably chemical, to the undamaged endocardium in the absence of myocardial disease.

CARCINOID HEART DISEASE

It would be superfluous to do more than mention carcinoid heart disease, since it is the subject of such current interest.[130] The endocardium of the heart valves and walls on the right side are most usually involved, although the heart valves on the left can be affected, if more mildly. On the endocardium is deposited a curious form of fibrous tissue devoid of elastic fibers, so that elastica stains show quite clearly that the tissue is deposited on the existing intact endocardium, even though the latter tissue may contain many mast cells.[131] Some of the mural lesions may represent only secondary fibroelastosis, but others are of the same nature as the valvular lesions, and do not occur apart from the valvular lesions. In many cases there is no evidence of underlying myocardial disease. There seems to be little doubt that the cause of this condition is the liberation of 5-hydroxytryptamine from hepatic tumor deposits, but the precise way in which this damages the endocardium is not known. Thorson[132] has considered the relationship of this disease to endomyocardial fibrosis, and it is evident that the lesions are pathologically quite distinct, as they certainly are etiologically (despite the high content of serotonin in the bananas which are so widely consumed in Uganda). Other investigators have dwelt on the dissimilarity of this lesion from all other forms of heart disease, its importance in this discussion being that it shows how a chemical attack can damage previously normal endocardium, and not cause fibroelastosis.

CARDIAC LESIONS IN THE "COLLAGEN DISEASES"

The subject of cardiac lesions in cases of the collagen diseases has elicited great interest in recent years. In general, cardiac lesions occur only as part of a systemic disease with involvement of many organs and tissues. Either the myocardium or the arteries bear the brunt of the damage, and if the endocardium is damaged, it is usually the valvular endocardium. The exception is found in cases of systemic lupus erythematosus, in which verrucose mural endocardial lesions occur with marked fibrinoid necrosis, cell damage, and platelet accumulation.[133] Such lesions are reported less commonly than heretofore.[134] They are focal and seem to have no particular predilection to affect any specific areas of the endocardium. In the other diseases the mural endocardium is not specifically affected, but only secondarily to myocardial damage. Where severe, there may be a compensatory fibroelastosis causing some widespread endocardial lesions, but usually such lesions are also focal. They bear no relation to the lesions of endomyocardial fibrosis, they have not the widespread nature of the lesions seen in Becker's disease, and they are dissimilar to the cardiac lesions of Löffler's disease, although arteritis is a feature of both. It is, in fact, the massiveness and severity of the cardiac lesions in the three main diseases under discussion which is in such contrast to the cardiac lesions of the collagen diseases.

POSTPARTUM HEART DISEASE

Postpartum heart disease has been described under a variety of names; it is a condition of congestive heart failure, often with embolic complications, occurring in puerperal women.[135-138] Benchimol and associates[139] have recently reviewed this condition and believe that it is not a specific entity, but one which covers five main groups, classified according to etiology. Their second group, in which they consider toxemia of pregnancy to be a factor of importance, is more closely reminiscent of the cases generally grouped under this heading, i.e., those with sustained hypertension and embolic phenomena. The emboli arise from thrombi on the mural endocardium which show a variable amount of organization; the myocardium shows foci of degenerating myocardial fibers and a moderate cellular infiltration with lymphocytes and macrophages and fibrotic replacement. Hydropic degeneration may be prominent, and in one case there was a severe pancreatitis, not dissimilar to that found by Stemmermann[74] in a case of endomyocardial fibrosis.

The cause of this condition is unknown, but it seems that a number of patients eventually recover. It appears, regrettably, that no one has yet recorded the subsequent autopsy findings in a recovered case.[140] It would be interesting to know the ultimate fate of these individuals.[141]

HEART DISEASE IN ANIMALS

So far, neither the experimental animal nor the casual observations made in animals have contributed much toward the solution of the problems raised by these obscure diseases affecting the mural endocardium. In this field there would seem to be a sad lack of liaison between pathologists in the field of human

diseases and their veterinary colleagues. Endocardial fibroelastosis has recently been recorded in animals, but nothing that was quite comparable to these other disease syndromes. Yet there are a number of diseases known to veterinarians which should interest the pathologist in the field of human diseases who is concerned with these problems. They seem of obscure etiology, and the circumstances in which they occur appear to point to infectious causes, although in animals, true epidemics of nutritional or toxic-metabolic disease may occur. One such is the so-called "round heart disease" of poultry,[142] and the descriptions of the histologic changes in the hearts of these birds is reminiscent of those recorded in certain obscure cases of human cardiomyopathy.[143] The hearts are dilated and hypertrophied, there is vacuolation of the myofibers, with longitudinal fibrillation, fragmentation, and nuclear degeneration and interstitial edema, with a moderate cell infiltrate. No specific lesions are found in other organs. There may be fibrogenesis in the myocardium. Those who recover are presumably eaten and their heart lesions are unrecorded! (How reminiscent of some human cases in the literature.)

In pigs there occurs a form of acute heart failure of unknown etiology in which the hearts are dilated and hypertrophied and the ventricles contain massive thrombi which cause embolic accidents.[144] It may follow pregnancy. Little seems recorded of the detailed histopathologic changes. The matter cannot be pursued here, but more cooperation with veterinary colleagues might teach us more about these obscure heart diseases in human beings.[145]

CONCLUSIONS

This review can only be regarded with dissatisfaction, for although many questions are raised, few if any are answered. Most attention has been devoted to endocardial fibroelastosis (Becker's disease, Löffler's disease, and endomyocardial fibrosis), and I have endeavored all through to emphasize the great differences between these entities which have been so often confused and muddled together. It seems to me that these differences are so great that they altogether outweigh the similarities, and I think much is to be lost and little gained if these entities are not clearly defined and separated. Some of the main differences are shown in Table I, and these differences may be of crucial importance in helping us to search for etiologic factors in these obscure diseases. I would plead for less terminological inventiveness and argument and for more detailed and meticulous study of these cases of obscure cardiomyopathy, both on the clinical and the pathologic side and in both man and animals.

Writing this review has entailed the reading and pondering of many case reports which I have found it difficult, if not impossible, to classify. My study has led me to consider what are the important points which should be established for each case of obscure endocardiomyopathy, and I would like to conclude by putting forward the following suggestions as to things that should, if possible, be established. The list of suggestions is weighted toward the anatomic side, where my own interests lie, and is not exhaustive, so that any clinician or pathologist will be able to improve upon it. It does include what I think are the es-

sentials. I should perhaps add that I am conscious of my own shortcomings in this respect, and, like many pathologists, I regard with suspicion all pro-formae drawn up by others.

The points are: (A) Clinical course with special reference to: (1) the frequency of embolic phenomena; (2) the absence or presence and duration and intensity of eosinophilia in the blood, and if present, special attention to a search for possible specific causes; (3) any evidence of generalized vascular disease especially affecting the central nervous system, the kidney, or the liver; (4) the continued or the episodic nature of the disease and the changes in the body and its fluids which may be associated with different phases of the disease; (5) the response to treatment and the duration of the illness; (6) the onset of the disease, with reference to febrile episodes, nutrition, etc. (B) Autopsy examination with special reference to: (1) the exact sites and extent of the endocardial thickening; (2) the nature of the tissue at the junction of the inflow and outflow tracts; (3) the extent and type of valvular involvement, with special attention to the mural endocardium behind the posterior leaflets of the A-V valve; (4) the coronary vessels and the great vessels; (5) the presence or absence of congenital defects; (6) the extent and distribution of visible myocardial fibrosis, with special attention to the subendocardial region. (C) Microscopic examination with special reference to: (1) the identification, if possible, of the original endocardium; (2) the presence or absence and the degree, extent, and distribution of any elastosis; (3) the presence of any thrombus, its nature, and degree of organization and incorporation; (4) the nature of the junctional layer between the abnormal endocardium and the myocardium; (5) the degree and type of connection between endocardial and any myocardial fibrosis, and the site, extent, and nature of the latter; (6) the condition of the Thebesian veins, arterioluminal and other vessels; (7) the type of change, if any, in the myofibers and interstitial tissue, with special attention to the distribution of lesions in relation to arterial supply and the endocardium, especially if hydropic degeneration is present; (8) the type, degree, and extent of any cellular infiltrate.

Were this knowledge available in all cases, progress might be made more quickly in our understanding of these obscure diseases, and the hoped-for goal of prevention nearer to our sight.

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Annotations

The Postmyocardial Infarction Syndrome

Pericarditis accompanying acute myocardial infarction is generally considered to be an insignificant feature. Its sole clinical manifestation, it is felt, is a pericardial friction rub which is heard in the first few days following the coronary attack and is characteristically fleeting. When later in the course of the illness, fever and chest pain recur, extension of the myocardial infarction or pulmonary embolism are usually diagnosed. The validity of these diagnoses has been recently questioned by a new concept which gave the clinical observations a different meaning. It was pointed out that prolonged and recurrent chest pain and fever are frequently caused by pericarditis, which may form a major complication of myocardial infarction, causing a protracted and sometimes stormy illness. Pericarditis is often associated with pleuritis and pneumonitis. The complication was referred to as "postmyocardial infarction syndrome" (PMIS).[1,2] The new concept was corroborated by a number of clinical reports.[3-6,12-17]

A tendency to recurrences is an outstanding feature of the PMIS. In this as in other regards it closely resembles the postcommissurotomy syndrome, to which it is probably related etiologically. The PMIS complicates approximately 3 per cent of the cases of acute myocardial infarction. It develops within from 1 to 8 weeks of the coronary attack. Its duration varies from a week to several months, depending on the number of recurrences. The complication is apparently benign.

The pericardial and pleural exudates, as well as the pneumonitis, are sometimes intensely hemorrhagic, even in the absence of anticoagulant therapy.[7,8] The latter fact needs to be emphasized because there has been a tendency to attribute hemorrhagic complications of myocardial infarction to the use of anticoagulants.[9,10] Yet, the clinical features of the cases reported as hemopericardium complicating myocardial infarction almost invariably fit the picture of the PMIS. Hemorrhagic pneumonitis which sometimes develops within a few days of the myocardial infarction is usually diagnosed as pulmonary infarction.

The etiology of the PMIS is unknown. No bacterial growth was obtained from cultures of blood and exudates; nor was it possible to alter the clinical course by the use of antibiotics. It was suspected that the PMIS may be due to sensitization, perhaps by antigens resulting from myocardial necrosis. This view seems to find support in some clinical observations. Corticosteroids invariably cause dramatic improvement. Their withdrawal is often followed by rebounds. In one instance, recurrence of pericardial effusion was observed after 2 years of steroid therapy when the hormones were withdrawn.[11] In a few cases the PMIS was associated with eosinophilia, arthritis, and indolent subcutaneous nodes.

Since the PMIS is usually a self-limited condition, in many instances no therapy is required other than the use of salicylates, codeine, or Demerol. When the complication is unduly prolonged or marked by intractable pain, or when pneumonitis causes a stormy course, administration of corticosteroids is justified. Extreme caution is indicated in the use of anticoagulant therapy because of the danger of hemorrhage and cardiac tamponade when there is evidence of generalized pericarditis.

The PMIS is sometimes diagnosed as idiopathic pericarditis,[18] when the preceding coronary episode has been silent or caused only minor symptoms and signs; and, especially, when a period of from 6 to 8 weeks has elapsed between recognition of the pericarditis and the acute coronary

episode, so that the causal relation of the two conditions is obscured. It is a good rule, therefore, in any given case of pericarditis of unknown etiology to include "coronary origin" among the possible etiological factors to be considered. Such a diagnostic consideration is apt to narrow the field of "idiopathic" pericarditis.

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Osler's Nodes

Among the cutaneous manifestations of bacterial endocarditis, Osler's nodes are a curious and dramatic diagnostic sign of the disease. First described in 1893, by Sir William Osler,[1,2] these peculiar red-purple, swollen, slightly raised cutaneous nodules are seen chiefly at the tips of the fingers and toes, and less often on the thenar or hypothenar eminences and the sides of the fingers or toes. They are usually heralded by the onset of pain at the site at which the discoloration is to appear several hours or a day later. They vary in size from a millimeter to a centimeter or more; their color is red-purple, with a blanched center at times; and their duration is from hours to several days.[3,4]

Osler's nodes were originally considered to represent embolic phenomenon,[5] but biopsy studies emphasized the absence of emboli or bacteria, and described endothelial swelling as due

to perivasculitis in many tiny vessels lying beneath the Malpighian layers.[6-8] Occasionally, necrosis was seen in the center of the lesion. One study reported involvement of reticuloendothelial and perineural elements as well as the endothelial and perivascular tissues. Overlying skin is normal, but ulceration is known to have occurred. The most generally accepted theory considers these lesions to be allergic reactions to the etiologic agent of the disease.

Libman[9] thought these nodes to be pathognomonic of subacute bacterial endocarditis (lenta), but many others insist upon having seen them in typhoid fever, gonorrhea, and lupus erythematosus as well as in endocarditis due to hemolytic, nonhemolytic and gamma streptococci, staphylococci, gonococci, *Hemophilus influenzae*, and diphtheriae.[5,7,10]

The incidence is greatest in cases of endocarditis lenta (50 per cent), and it ranges down to 16 per cent[10] in series of mixed etiological conditions.

Osler's nodes have often been a deciding factor in diagnosing bacterial endocarditis when other classic signs and symptoms were lacking.

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Vasomotor Nerves to Human Skin

If a subject immerses his feet and calves in warm water, a conspicuous increase in blood flow subsequently occurs in the hands and forearms.[1,2] This does not occur if the upper limbs have been previously sympathectomized, indicating that sympathetic nerves are responsible for the changes in flow.[3] If methods are employed which allow simultaneous estimations of the contributions of skin and muscle vessels, it is found that the changes in flow are confined to the skin. For example, when skin and muscle blood flow in the forearm are simultaneously estimated by Hensel's heated thermocouples[4] or by changes in the oxygen saturation of effluent blood from superficial and deep forearm veins,[5] skin but not muscle blood flow increases during body heating. Furthermore, body heating fails to cause an increase in the blood flow of the forearm when the circulation in the skin is suppressed by adrenaline iontophoresis.[6] The "vasomotor centers" controlling skin vessels can thus function quite independently of those controlling muscle vessels.

Although the responses of the hand and of the forearm skin vessels to changes in body temperature appear to be similar, there is a different pattern of vasomotor control in the two areas. The blood vessels in the hand are normally subject to a high degree of vasoconstrictor tone. Blocking the nerves to the hand with local anesthetic normally increases the blood flow through the hand to about 30 to 40 ml. per 100 ml. per minute. The very large increase in blood flow in the hand during body heating seems to be due entirely to the release of vasoconstrictor tone. Despite the evidence for vasodilator nerves in patients with Raynaud's disease,[1] careful investigation has failed to provide any evidence for such fibers in the hands of normal individuals. During body heating the blood flow in a normal hand does not exceed that in a nerve-blocked hand,[7-11] and

atropinization of the hand by intra-arterial infusion of the drug fails to reduce the vasodilatation.[9,12] However, acetylcholine has been obtained from extracts of human digital arteries,[14] and cholinesterase has been identified in sections of digital skin.[15] Recently, Barcroft and associates[15] have found an increase in the flow of blood in the hands of subjects exposed to emotional stress. It is possible that cholinergic fibers to the blood vessels of the hand, if they do exist, are activated in response to emotional rather than thermal stimuli, and only come into play during body heating if the heating causes stress. It has been suggested that this type of vasodilatation may be associated with emotional sweating.[15]

In the skin of the forearm, when the subject is comfortably warm, the vessels are not subject to any appreciable vasoconstrictor or vasodilator tone. When the cutaneous nerves to the forearm are blocked under these conditions, there is little change in flow.[3,16-18] In response to body heating the vessels of the skin dilate because of the activity of cholinergic dilator nerves, and in response to body cooling they constrict because of the activity of vasoconstrictor nerves. The pattern of vasodilatation in the forearm during body heating differs from that in the hand. If the subject is initially cool, the increase in the blood flow in the forearm occurs in two phases.[12] The first increase, a very small fraction of that attainable by heating, occurs synchronously with the precipitous increase in the blood flow of the nand. The increase, like that in the hand, is unaffected by atropinization of the tissues, and it is likely that it is due to release of vasoconstrictor tone. The second phase of the forearm vasodilatation, which comprises the major part of that attainable by heating, occurs at a time when the blood flow in the hand has reached its maximum.[19] This phase occurs at about the time when sweating of the forearm commences. It does not occur if the sympathetic nerves to the skin of the forearm are blocked,[17,18] and it is reduced and delayed by atropinization of the forearm.[12] These findings indicate that the second phase of the vasodilatation is dependent, at least in part, on the activity of sympathetic vasodilator nerves.

The close association of the second phase with the onset of sweating suggested that the vasodilatation might be linked in some way to the activity of the sweat glands,[20] a situation analogous to that seen in the vasodilatation in the submandibular salivary gland.[21] There is now evidence that the vasodilatation in the skin of the forearm during body heating may be due to vasodilator substances released from the activated sweat glands rather than to the excitation of specific vasodilator nerve fibers. Fox and Hilton[20] have found that bradykinin-forming enzyme is produced in the skin during sweat-gland activity, and they suggest that the resultant formation of bradykinin (a polypeptide with vasodilator properties) contributes to the vasodilatation in skin during body heating.

The contrast between the vasomotor innervation of the skin of the hand and that of the skin of the forearm emphasizes the danger of making general deductions about the vasomotor control of skin vessels from experimental findings made in one area of the body. Most of the skin of the body is completely uncharted as regards vasomotor innervation, and these areas will have to be explored before a complete picture can be obtained.

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Acute Rheumatic Fever in Adults

Friedberg[1] has recently pointed out the rarity of acute rheumatic fever in adults over 25 years old who have not previously had the disease. The diagnosis is frequently made on the basis of arthritis alone. The finding of subcutaneous nodules, erythema marginatum, and chorea is very rare. A diagnosis of rheumatic carditis is also difficult to establish in adults, since other forms ot heart disease are common. Friedberg believes that rheumatic carditis can be diagnosed only when a diastolic murmur appears under observation. He also challenges the concept that Aschoff bodies are evidence of clinically active rheumatic fever, since there is poor correlation between clinical status and the pathologic findings in auricular biopsies taken at operation.

All of these difficulties in making a diagnosis of acute rheumatic fever in adults are considered in a paper by Pader and Elster.[2] Using the rather strict criteria of Friedberg, a good many of the 30 patients reported would not qualify for a diagnosis of acute rheumatic fever, and the authors suggest that the Jones criteria for the diagnosis of rheumatic fever in children be liberalized when applied to adults.

The main stumbling block is the diagnosis of rheumatic carditis. A prolongation of the P-R interval, changing murmurs, a pericardial friction rub, an enlarged heart, or heart failure are not specific signs of acute rheumatic carditis and can be interpreted only tentatively.

One further concept of Friedberg is of great interest. He states that he has never seen a patient who developed his first attack of rheumatic fever after the age of 25 who has gone on to develop rheumatic valvular damage. Unfortunately, there are reports in the literature of patients developing their first attack as an adult, with progressive involvement of the heart valves and death from heart failure. What we do not know is how often this occurs. If it is as infrequent as

Friedberg suggests, this is added evidence that there are significant differences between acute rheumatic fever in children and that in adults.

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Classification of Systolic Murmurs

The advantages of careful clinical auscultation of the heart are frequently forgotten, due in part, perhaps, to the feasibility of precise physiologic studies. In the current literature, systolic murmurs are frequently described in the classic descriptive terms of intensity, location, radiation, and quality, but without mention of duration. Leatham[1,2] first proposed a classification of systolic murmurs into two types: ejection and pansystolic.

Ejection systolic murmurs are found in conditions associated with increased turbulence of blood flow through the semilunar valves. Blood flow through the semilunar valves does not occur throughout the whole of systole, but is limited to the period of systolic ejection. Thus, the ejection murmur starts slightly after the first sound, the delay corresponding to the period of isometric contraction. The murmur is loudest during the period of maximal ejection in mid-systole, and diminishes as intraventricular pressure falls and flow through the valves declines. It ceases before the second sound.

Aortic ejection murmurs are found classically when there is aortic stenosis, but also in aortic valvular deformity without stenosis, subvalvular stenosis, dilatation of the aorta, and increased aortic flow.

The ejection systolic murmur of pulmonary stenosis is a little more difficult to recognize,[3] because it is frequently longer and its relation to the second sound is complicated by the fact that the second (pulmonary) component of the second heart sound is usually absent, allowing the pulmonary ejection murmur to persist until the onset of the first (aortic) component of the second heart sound. This illusion of the murmur persisting to the end of systole will not deceive the auscultator who pays to the second heart sound in the pulmonary area the strict attention that it deserves.[4] The features of onset slightly after the first heart sound and mid-systolic accentuation are further aids in the recognition of the pulmonary ejection murmur. A pulmonary ejection murmur is found in atrial septal defect because of the greatly increased flow through the pulmonary artery and the dilatation of that vessel.

An ejection systolic murmur at both pulmonary and aortic areas may be heard in complete heart block (increased stroke volume), as well as in such conditions as fever, anemia, and thyrotoxicosis. Phonocardiography records a slight ejection murmur in most normal individuals, and the exaggeration of this phenomenon accounts for many innocent murmurs. Other varieties of the innocent systolic murmur[5] are the apical late systolic murmur and the short, low-pitched murmurs frequently audible at the lower left sternal edge.

In contrast to the ejection murmurs which by their very nature are limited to the period of systolic ejection, other murmurs are due to abnormal flow that occurs throughout the whole of systole, and they are, therefore, pansystolic. In mitral and tricuspid incompetence there is a pressure gradient between ventricle and atrium, with regurgitant flow and murmur all through systole. The pansystolic or regurgitant murmur of atrioventricular valve incompetence, therefore, begins with the first heart sound and ends with the second sound. This situation is in marked contrast to that which obtains at the semilunar valves, where gradient, flow, and murmur are confined to the period of systolic ejection. Similarly, in uncomplicated ventricular septal defect the pressure gradient between the left and right ventricles is present throughout systole and, in consequence, the flow and the murmur are pansystolic. This pansystolic murmur can be differentiated clinically

from the pulmonary ejection murmur of atrial septal defect, tetralogy of Fallot, pulmonary stenosis, and from that of ventricular septal defect with pulmonary hypertension and little, if any, left-to-right shunt.

The machinery type of murmur of patent ductus arteriosus is greatly modified when there is pulmonary hypertension as well. The diastolic component is diminished, but the systolic murmur that persists may retain its "continuous" nature, that is, it is accentuated in mid and late systole and persists beyond the second component of the second heart sound. When the left-to-right shunt ceases altogether, this classic systolic murmur is replaced by the pulmonary ejection murmur of dilatation of the pulmonary artery.

In practice, it is usually possible to distinguish between the murmurs of atrial and ventricular septal defect. The murmurs of mitral incompetence and aortic stenosis can be differentiated and this is particularly helpful when the aortic systolic murmur is as loud at the apex as it is at the base, or louder. Unfortunately, this distinction is often exceedingly difficult to make, even with the aid of phonocardiography, when aortic stenosis and mitral incompetence are both present, because the two murmurs interfere with each other.

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Book Reviews

CLINICAL SCALAR ELECTROCARDIOGRAPHY (Fourth Edition). By Bernard S. Lipman, A.B., M.D., F.A.C.P., Associate in Medicine, Emory University School of Medicine; Consultant, Glenville Giddings Cardiac Clinic, St. Joseph Infirmary; Consultant, Cardiac Clinic, Grady Memorial Hospital; Regional Consultant in Cardiology to the Veterans Administration, Atlanta, Ga.; and Edward Massie, A.B., M.D., F.A.C.P., Associate Professor of Clinical Medicine, Washington University School of Medicine; Director of Heart Stations, Barnes Hospital and Jewish Hospital, St. Louis, Mo.; Director, Cardiovascular Clinic, Washington University Clinics; Area Consultant in Cardiology to Veterans Administration. Chicago, 1959, Year Book Publishers, Inc., 438 pages. Price $8.00.

The original book by the authors, which appeared under the title *Clinical Unipolar Electrocardiography*, in 1951, has had two editions and three reprintings since that time. The popularity of the book, which was intended as a brief introduction to electrocardiography for the beginner, was due to its practical approach and to the brevity and simplicity of presentation, which at the same time included all of the most important basic concepts founded on the fundamental work of Einthoven, Lewis and Wilson. In the present edition the authors have tried to present also some of the more controversial modern concepts, including the ionic mechanisms of cellular excitation, without deviating from their original plan. The change in the title was meant to indicate that the book discusses the standard as well as the unipolar limb leads, but the orthogonal leads used in vectorcardiography, as well as the vectorial approach, are adequately discussed in a separate chapter. Some of the new additions include peri-infarction and focal blocks, the ventricular and atrial overload syndromes, the U wave, parasystole and re-entry, and other arrhythmias. The number of original electrocardiograms included in the appendix of the book, as well as the number of references, has been greatly enlarged. In general, the present edition represents a great improvement over the previous ones. The only improvement still to be desired is a more realistic reproduction of some of the hand-drawn electrocardiographic patterns scattered throughout the text.

HYPERTENSION (The First Hahnemann Symposium on Hypertensive Disease). Edited by John H. Moyer, M.D., Professor and Chairman, Department of Medicine, Hahnemann Medical College and Hospital; with the assistance of John R. Beem, M.D., Joseph DiPalma, M.D., Wm. Likoff, M.D., Robert Bower, M.D., Arthur Grollman, M.D., and Lewis C. Mills, M.D., Philadelphia and London, 1959, W. B. Saunders Company, 790 pages. Price $14.00.

This book is a collection of 79 presentations given at a symposium which took place in December, 1958. In addition to the individual presentations, it contains 17 discussions and two concluding panel discussions dealing with the effect of therapy on prognosis and with recommendations for drug therapy. The contributions are divided into five groups: I. Pathology and Clinical Aspects of Hypertension. II. Basic Concepts of the Etiology of Hypertension. III. Pharmacology of Hypertension and Use of Sympathetic Blocking Agents. IV. The Use of Salt and Diuretics and Special Problems in the Therapy of Hypertension. V. The Surgical Approach to Essential Hypertension.

As would be expected from the number of contributors (91), the reader is provided with a representative cross section both of current opinion regarding therapy and of approaches to the study of pathogenesis which were then engaging the attention of investigators. There is little of the material presented which has not been published elsewhere. However, any reader of the book is likely to be unfamiliar with some of the interesting contributions, and for all it brings together material scattered throughout a number of journals. Also, in the discussions, areas of disagreement and uncertainty are brought into clearer focus than is usual with monographs by a single author.

To this reviewer, the most interesting chapter in Part I was that by Phyllis Hartroft and her co-workers, describing their studies of the renal juxtaglomerular cells. They have presented further evidence that sodium depletion causes hyperactivity of the zona glomerulosa of the adrenal as well as hyperactivity of the juxtaglomerular cells of the kidney. The latter change takes place in adrenalectomized animals, and Hartroft suggests the possibility that the juxtaglomerular cells are capable of humorally stimulating the zona glomerulosa.

In Part II, dealing with basic concepts in etiology, the old problem of renal hypertension is briefly reviewed by Grollman. Then, both parts of the adrenal, the liver, sodium, stress, trace metals, and monoamine oxidase are discussed in turn. The exchange of opinions on etiology brought out the still unresolved conflict between the proponents of the primacy of renal vascular changes in essential hypertension and those who consider them to be secondary.

Part III contains two chapters by Paton which are outstanding. One is a succinct review of the pharmacology of blocking agents, and the other is a stimulating discussion of the rationality, or irrationality, of ganglionic blocking agents in hypertension. In the latter, he assumes the role of advocate for the view that essential hypertension is neurogenic in origin. After marshaling the evidence for the neurogenic hypothesis, he admits that ganglionic block cannot be the ideal treatment, ". . . since no one believes that the autonomic overactivity arises in the ganglia. The great question, indeed, is how does it arise? Is it by changes in the baroreceptor organs, or by an abnormality in the 'set' of the vasomotor center, or by psychological maladjustment, or by some structural abnormality of the central autonomic pathways allowing them to reverberate, like an obsessive memory, when they should have sunk to quiescence?" The abnormality of the "set" of the vasomotor center referred to by Paton was long ago ascribed by Leonard Hill to a defective blood supply to the brain stem, and this idea was revived by Ernest Starling after his classic experiments showing control of blood pressure by varying the blood flow to the head of the dog. This old hypothesis has recently received strong support from a postmortem study by Dickinson and Thomson, in which a surprisingly good inverse correlation was demonstrated between blood pressure during life and flow through the vertebral arteries under a fixed perfusion pressure. This new evidence would seem to enhance the attractiveness of Paton's position, with the important difference that the ultimate culprit is once again vascular.

Over 400 pages of the book are devoted to therapy, or to pharmacology of therapeutic agents. It must suffice to say that there is no important treatment or agent which was available at the time of the symposium that has not been discussed. Individual differences in choice of drugs are made evident, and it is clear that blocking agents are still the mainstay in an effective regimen for severe hypertension without renal failure. What is missing in such brief presentations are the minute particulars of everyday management with these potent agents, which can make the difference between success and failure. Of particular interest to cardiologists was the agreement among several contributors that heart failure had virtually disappeared as the sole cause of death in adequately treated hypertensive patients.

As intimated above, the book contains "something for everybody" and is recommended to anyone interested in hypertension. Its permanent value will be as an index of our knowledge and ignorance, minor triumphs, and major frustrations as of 1958.

HIGH BLOOD PRESSURE. By Eugene B. Mozes, M.D., Philadelphia, 1959, J. B. Lippincott Company, 186 pages. Price $1.45 (paperbound).

This little book has a great deal of information which will be of interest to the patient with high blood pressure. In the reviewer's opinion a book of this type should serve primarily to allay apprehension and to correct misconceptions. This book goes a long way in this direction by de-

bunking many of the erroneous ideas held by the average layman. The reviewer himself did not realize that myocardial infarctions were no more common in hypertensive patients than in people with a normal blood pressure. However, the statement that strokes are more common in hypertensive people will surely increase apprehension. This perhaps could be allayed somewhat by the statement that the high pressure itself does not cause many cerebral accidents, but that it is the arteriosclerosis which is associated with the hypertension which produces the accident. The development of arteriosclerosis may take 20 to 40 years after the onset of the hypertension. If the reader believes that patients are better off with a detailed knowledge of hypertension, this book may be recommended. However, I would suggest that the physician read the book himself before suggesting it to patients, for two reasons: (1) there may be information here which had better be left unsaid to certain individuals, and (2) the book may raise questions in the minds of patients which will require answers from the physician and he must be prepared.

ELECTRICAL IMPEDANCE PLETHYSMOGRAPHY. THE ELECTRICAL RESISTIVE MEASURE OF THE BLOOD PULSE VOLUME, PERIPHERAL AND CENTRAL BLOOD FLOW. (A monograph in the Bannerstone Division of American Lectures in Medical Physics.) By Jan Nyboer, D.Sc., M.D., Chief, Division of Cardiovascular Physiology Research; Electrocardiographer and Associate Physician, Department of Medicine Harper Hospital, Detroit, Mich.; Professor, Department of Physiology and Pharmacology, Wayne State University Medical School, Detroit, Mich. Springfield, Ill., 1959, Charles C Thomas, Publisher; Oxford, England, Blackwell Scientific Publications, Ltd.; Toronto, Canada, Ryerson Press, 243 pages. Price $7.50.

This monograph summarizes in an orderly fashion the thoughts and work which the author has developed during the past 20 years. Fundamental principles for the measurement of segmental volume conductors by electrical resistance are defined, and full discussions of the instruments and possible applications are included. Aspects of impedance plethysmography are well presented, but physicians will find the mathematic and physical arguments to be difficult.

Because many have doubted the accuracy of the impedance method as a technique for measuring the volume of flow, the author presents data in support of the procedure. Plethysmography is an important method for studying the peripheral circulation, and the impedance method is a relatively simple procedure. Therefore, Nyboer's method can prove to be useful to investigators and clinicians if it can be made quantitatively accurate. The apparatus is rugged and the procedure sufficiently reliable for many applications if adequate attention is given to details. Any differences that the method may have in comparison with the mechanical methods are of no great significance for many physiologic investigations, but the method is not so reliable quantitatively as are other methods. This is evident from the monograph. For example, the investigator must decide for himself whether or not the differences between the curves recorded mechanically and those recorded electrically, as shown in Figure 36, page 88, are important. Of course, the accuracy of the mechanically recorded trace is doubtful for the method of recording blood flow in a segment of the digit of man as used by Nyboer to evaluate his own method (Figure 31, page 82). The run-off slopes of the curves recorded simultaneously by the mechanical and impedance methods, as illustrated in Figure 37, page 89, are quite different and may reflect the limitation of the impedance method for quantitative studies which demand a high degree of accuracy. Again, as mentioned above, the mechanical method employed in the evaluation of the electrical method may be in error to an unknown degree in an unknown direction.

Nyboer's reasoning in support of his method for the measurement of outflow, as outlined on pages 95 to 102, is difficult to follow and is not convincing to this reviewer. On page 95 the author states: ". . . . after closure of the aortic valves, the segmental pulse volume is dependent on the venous drainage from the given segment." The venous drainage, however, occurs not only during diastole but throughout the pulse cycle. Blood flows into and out of the segment during systole and diastole. In fact, outflow is greater in magnitude during systole than during diastole. Nyboer's method for measuring outflow is of a special nature and does not appear to measure outflow only, even with arterial occlusion and a study of the run-off slope. For example, on page 97 item "g" states: "If there is complete occlusion to arterial inflow to the segment, the segmental volume will then diminish in proportion to the amount of previously stored blood in the segment and the

remaining hindrance to outflow." This statement is difficult to understand unless arterial occlusion is made just proximal to the impedance recorder and the venous drainage is backward or is into the collecting vessels located distal to the recorder. Such reversal of venous flow is unlikely with valves present in the veins. If the arterial occlusion is made at a great distance proximal from the impedance electrodes to allow for adequate vessels for collecting the flow out of the segment in a proximal direction, other blood will be flowing into the segment from both proximal and distal portions of the part under study. Such details must be carefully evaluated by one proposing to use the method. It would be difficult even to measure the amount of blood remaining in a segment in order to test the idea. Unfortunately, other rather loose generalizations are made on page 97. The author fails to acknowledge the fact that simultaneous time-course curves of inflow and outflow have been developed elsewhere, and some of his ideas have not only been tested but answered.

In the final chapter, use of the impedance method for the measurement of segmental flow through the use of the Stewart-Hamilton principle is discussed. This application of the method is an interesting one and can prove to be useful, although the accuracy of the method proposed is difficult to estimate.

Nyboer has supported the monograph with a good bibliography. It is helpful to have a summary of Nyboer's work in a single volume. Those studying the peripheral circulation will find the book interesting, although the presentation will at times be difficult for those without a good knowledge of mathematics and electricity. The reader is warned, however, to carefully consider the arguments presented by the author and not to accept them without critical thought, since he will not be able to agree with many ideas. This book is not for beginners or clinicians who are not experts in the field.

REACCIONES ELEMENTALES DE LA PARED ARTERIAL FRENTE A LAS INJURIAS Y EN SU RELACIÓN CON LA ETIOPATOGENIA DE LA ATEROESCLEROSIS. Tesis doctoral por Emiliano Roda Pérez, 258 pages.

In this book the author attempts to analyze the problem of arteriosclerosis from the histologic, metabolic, and experimental point of view. His review with regard to the histology of the vessels and the metabolic changes that are related to arteriosclerosis, although based on an extensive bibliography, is not critical. Many pages of this book are devoted to the physiology of blood pressure control and the role of catecholamines as vasoactive materials. This discussion has very little connection with the proposed problem of arteriosclerosis. The histopathologic concept of atherosclerosis is not well delineated as opposed to the other arteriopathies. For this reason, in the chapter on experimental work, the author's methods and conclusions are misleading to the reader. Lathyrism, experimental hypertension, and bilateral nephrectomy are discussed with reference to their associated vascular lesions and their probable role as pathogenic factors leading to, or enhancing, the process of arteriosclerosis. The number of animals used in each experiment is relatively small, and makes it difficult or unwise to draw conclusions. In summary, it does not appear that the problem of arteriosclerosis is properly approached and adequately analyzed in this book.

A PRIMER FOR CORONARY PATIENTS. By R. J. Needles, M.D., and E. M. Stoney, New York, 1958, Appleton-Century-Crofts, Inc., 176 pages. Price $3.75.

This book was designed with the lay reader in mind. In that respect it is a useful book for the practicing physician to recommend to some of his patients with coronary artery disease. The material is presented lucidly and in such a manner that it is not likely to be misinterpreted by the patient. The author is very careful to avoid ambiguous and misleading statements. One may argue concerning the desirability of cardiac patients reading about their disease; however, in this day and age, one can scarcely avoid the great deal of literature which is being published on heart disease. Much of this material is incomplete and deals only in half-truths. Therefore, a work for the lay reader which brings together information concerning coronary artery disease and presents it in an orderly and understandable fashion is highly desirable. This book does precisely that.